JCD

JOURNAL WATCH

Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points—a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine

Børge G. Nordestgaard et al. European Heart Journal Advance Access published April 26, 2016 doi:10.1093/eurheartj/ehw152

This consensus critically evaluated the clinical implications of the use of non-fasting rather than fasting lipid profiles and to provide guidance for the laboratory reporting of abnormal non-fasting or fasting lipid profiles. Extensive observational data, in which random non-fasting lipid profiles have been compared with those determined under fasting conditions, indicate that the maximal mean changes at 1–6 h after habitual meals are not clinically significant [+0.3 mmol/L (26 mg/dL) for triglycerides; 20.2 mmol/L (8 mg/dL) for total cholesterol; 20.2 mmol/L (8 mg/dL) for LDL cholesterol; +0.2 mmol/L (8 mg/dL) for calculated remnant cholesterol; 20.2 mmol/L (8 mg/dL) for calculatednon-HDL cholesterol]; concentrations of HDL cholesterol, apolipoprotein A1, apolipoprotein B and lipoprotein (a) are not affected by fasting/non-fasting status.

In addition, non-fasting and fasting concentrations vary similarly overtime and are comparable in the prediction of cardiovascular disease. To improve patient compliance with lipid testing, we therefore recommend the routine use of non-fasting lipid profiles, while fasting sampling may be considered when non-fasting triglycerides .5 mmol/L (440 mg/dL).

For non-fasting samples, laboratory reports should flag abnormal concentrations as triglycerides ≥2 mmol/L (175 mg/dL), total cholesterol ≥5 mmol/L (190 mg/dL), LDL cholesterol≥3 mmol/L (115 mg/dL), calculated remnant cholesterol ≥0.9 mmol/L (35 mg/dL), calculated non-HDL cholesterol≥3.9 mmol/L (150 mg/dL), HDL cholesterol ≤1 mmol/L (40 mg/dL), apolipoprotein A1 ≤1.25 g/L (125 mg/dL), apolipoprotein B ≥1.0 g/L (100 mg/dL), and lipoprotein (a) ≥50 mg/dL (80th percentile); for fasting samples, abnormal concentrations correspond to triglycerides ≥1.7 mmol/L (150 mg/dL).

Life-threatening concentrations require separate referral when triglycerides .10 mmol/L (880 mg/dL) for the risk of pancreatitis, LDL cholesterol .13 mmol/L (500 mg/dL) for homozygous familial hyper cholesterolaemia, LDL cholesterol .5 mmol/L (190 mg/dL) for heterozygous familial hyper cholesterolaemia, and lipoprotein (a) .150 mg/dL (99th percentile) for very high cardiovascular risk.

Editor's comment:

The guideline recommends that non-fasting blood samples be routinely used for the assessment of plasma lipid profiles. Laboratory reports should show abnormal values on the basis of desirable concentration cut-points. Non-fasting and fasting measurements should be complementary but not mutually exclusive.

It is a fact that a person remains in fasting state for 6–8 hours only and both lipid and sugar surge occurs in the fed state. Post prandial abnormal blood glucose has been accepted as a major damage for cardiovascular complications. Now it is the time whether we should measure and standardise the post meal lipid levels for correlating with cardiovascular complications.

The Time is Right for a New Classification System for Diabetes: Rationale and Implications of the beta-Cell–Centric Classification Schema

Stanley S. Schwartz et al. Diabetes Care 2016;39:179–186 | DOI: 10.2337/dc15-1585

The current classification system presents challenges to the diagnosis and treatment of patients with diabetes mellitus (DM), in part due to its conflicting and confounding definitions of type 1 DM, type 2 DM and latent autoimmune diabetes of adults (LADAs). The current schema also lacks a foundation that readily incorporates advances in our understanding of the disease and its treatment. For appropriate and coherent therapy, we propose an alternate classification system.

The b-cell–centric classification of DM is a new approach that obviates the inherent and unintended confusions of the current system. The b-cell–centric model presupposes that all DM originates from a final common denominator-the abnormal pancreatic b-cell. It recognizes that interactions between genetically predisposedb-cells with a number of factors, including insulin resistance (IR), susceptibility to environmental influences, and immune dysregulation/inflammation, lead to the range of hyperglycemic phenotypes within the spectrum of DM. Individually or in concert, and often self-perpetuating, these factors contribute to b-cell stress, dysfunction, or loss through at least 11 distinct pathways. Available, yet under utilized, treatments provide rational choices for personalized therapies that target the individual mediating pathways of hyperglycemia at work in any given patient, without the risk of drug-related hypoglycemia or weight gain or imposing further burden on the b-cells.

Editor's comment:

The classification of diabetes has been changed several times. But still, it neither reflects the treatment nor the aetiology. This article proposes a classification assessing the beta cell status which can help us to choice our treatment. This is an urgent call for the review of the current DM classification system towards the consensus on a new, more useful system.

Blood glucose self-monitoring and internet diabetes management on A1C outcomes in patients with type 2 diabetes

Nelson Chow et al. *BMJ Open Diabetes Research and Care* 2016; 4:e000134. doi:10.1136/bmjdrc-2015-000134

The purpose of this study was to determine any correlation between frequency of self monitoring of blood glucose (SMBG), frequency of patient-provider communication of SMBG (reporting), and hemoglobin A1C for patients with Type 2 diabetes solely on oral medications.

191 charts of patients with type 2 diabetes treated solely with oral hypoglycaemic agents were reviewed retrospectively. A1C, SMBG frequency, and frequency of online communication with an endocrinologist within the most recent 6-month period were used in the analyses. Regression analysis was used to determine correlations to A1C. For subsequent subgroup analysis, patients were separated into infrequent and frequent SMBG groups, defined as those who test on average once or less per day or twice or more per day.

Although testing frequency did not correlate with A1C, higher reporting frequency correlated with lower A1C. Subgroup analysis of the frequent SMBG group showed a significantly lower A1C in frequent reporters when compared to infrequent reporters ($N=118$, $p<0.05$). This trend was not observed in the infrequent SMBG group ($N=73$, $p=0.161$).

The inverse correlation between reporting frequency and A1C, as well as the significant difference in A1C only for the frequent testers, suggests that frequent SMBG has an effect on reducing A1C only when combined with regular, frequent communication of SMBG with a healthcare provider.

Editor's comment:

It is not concluded whether frequent SMBG in T2 DM on oral drugs are essential or not. But it is a fact that SMBG should be always followed by dose adjustment. This study shows that frequency of self-monitoring of blood glucose is not found to affect A1c in non-insulin-dependent diabetes. Frequency of submission of online reports of blood glucose was found to be correlated with A1c and frequency of self-monitoring of blood glucose. For patients who tested frequently, a difference in A1c was found between reporting frequently and infrequently, where no difference was found in those who tested infrequently.

Effect of tighter glycemic control on cardiac function, exercise capacity, and muscle strength in heart failure patients with type 2 diabetes: a randomized study.

Roni Nielsen et al. *BMJ Open Diabetes Research and Care* 2016;4:e000202. doi:10.1136/bmjdrc-2016-000202.

In patients with type 2 diabetes (T2D) and heart failure (HF), the optimal glycemic target is uncertain, and evidence-based data are lacking. Therefore, we performed a randomized study on the effect of optimized glycemic control on left ventricular function, exercise capacity, muscle strength, and body composition.

40 patients with T2D and HF (left ventricular ejection fraction (LVEF) 35±12% and hemoglobin A1c (Hb A1c) 8.4±0.7% (68±0.8 mmol/mol) were randomized to either 4-month optimization (OPT group) or non-optimization (non-OPT group) of glycemic control. Patients underwent do but amines tress echo cardiography, cardiopulmonary exercise test, 6 min hall-walk test (6-MWT), muscle strength examination, and dual X-ray absorptiometry scanning baseline and at follow-up.

39 patients completed the study. Hb A1c decreased in the OPT versus the non-OPT group (8.4±0.8% (68±9 mmol/mol) to 7.6±0.7%(60±7 mmol/mol) vs 8.3±0.7% (67±10 mmol/mol) to 8.4±1.0% (68±11 mmol/mol); $p<0.001$). There was no difference between the groups with respect to changes in myocardial contractile reserve (LVEF ($p=0.18$)), oxygen consumption ($p=0.55$), exercise capacity ($p=0.12$), and 6-MWT ($p=0.84$). Muscle strength decreased in the non-OPT compared with the OPT group (37.2±8.1 to 34.8±8.3 kg vs 34.9±10.2 to 35.4±10.7 kg; $p=0.01$), in line with a non significant decrease in lean ($p=0.07$) and fat ($p=0.07$) tissue mass in the non-OPT group. Hypoglycemia and fluid retention did not differ between groups.

Editor's comment:

In patients with T2D and HF, intensified glycaemic control prevented deterioration in muscle strength, without increasing the incidence of hypoglycaemic events, fluid retention or affecting left ventricular contractile reserve and cardiopulmonary capacity. However, large-scale randomised trials evaluating clinical end points are needed. An increase in insulin dosage has no deleterious cardiovascular effects. An Hb A1c level of 7.5% seems to be a safe treatment goal in patients with T2D and HF.

Age-Specific Trends From 2000–2011 in All-Cause and Cause-Specific Mortality in Type 1 and Type 2 Diabetes: A Cohort Study of More Than One Million People DOI: 10.2337/dc15-2308.

Jessica L. Harding, Jonathan E. Shaw, Anna Peeters, Susan Davidson, and Dianna J. Magliano1. Diabetes Care Publish Ahead of Print, published online April 26, 2016

The objective of this study was to analyse changes by age-group in all-cause and cause-specific mortality rates from 2000–2011 in people with diabetes in Australia. A total of 1,189,079 (7.3% with type 1 diabetes) persons

with diabetes registered on the National Diabetes Service Scheme between 2000 and 2011 were linked to the National Death Index. Mortality rates in the total population were age standardized to the 2001 Australian population. Mortality rates were calculated for the following age-groups: 0 to <40 years, 40 to <60 years, and 60 to 85 years. Annual mortality rates were fitted using a Poisson regression model including calendar year as a covariate and age and sex where appropriate, with Ptrend reported.

For type 1 diabetes, all-cause, cardiovascular disease (CVD), and diabetes age standardized mortality rates (ASMRs) decreased each year by 0.61, 0.35, and 0.14 per 1,000 person-years (PY), respectively, between 2000 and 2011, Ptrend < 0.05, while cancer mortality remained unchanged. By age, significant decreases in all cause, CVD, and diabetes mortality rates were observed in all age-groups, excluding diabetes mortality in age-group 0–40 years. For type 2 diabetes, all-cause, CVD, and diabetes ASMRs decreased per year by 0.18, 0.15, and 0.03 per 1,000 PY, respectively, Ptrend < 0.001, while cancer remained unchanged. By age, these decreases were observed in all age-groups, excluding 0–40 years, where significant increases in all-cause and cancer mortality were noted and no change for CVD and diabetes mortality.

Editor's comment:

This is an interesting analysis on cause of death in diabetes, both type 1 and type 2. The group made a conclusion that all-cause, CVD and diabetes ASMRs in type 1 and type 2 diabetes decreased between 2000 and 2011, while cancer ASMRs remained unchanged. The improvement may due to better diabetes care and its effective implementation. However, younger populations are not benefiting from the same improvements as older populations either due to aggressive nature of the disease or lack of seriousness among the patients. But the absence of decline in cancer mortality warrants urgent attention.

Maternal Serum Prolactin and Prediction of Postpartum b-Cell Function and Risk of Prediabetes/Diabetes.

Ravi Retnakaran, Chang Ye, Caroline K. Kramer, Philip W. Connelly, Anthony J. Hanley, Mathew Sermer, and Bernard Zinman. Diabetes Care Publish Ahead of Print, published online April 26, 2016

The insulin resistance which develops in mid- to late pregnancy poses a physiologic stress test for the pancreatic beta-cells, which must respond by markedly increasing their secretion of insulin. This response is achieved through an expansion of beta-cell mass induced by the hormones prolactin and human placental lactogen (HPL). Conversely, the furan fatty acid metabolite 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF) has recently emerged as a negative regulator of b-cell function in pregnancy.

Because of their respective roles in the b-cell response to the stress test of gestational hyperglycaemia, the researchers hypothesized that antepartum prolactin, HPL, and CMPF may relate to a woman's underlying gluco-regulatory physiology and hence to her metabolic status after pregnancy.

Three hundred and sixty-seven women underwent measurement of fasting serum prolactin, HPL, and CMPF in the late-2nd/early-3rd trimester, followed by an oral glucose tolerance test (OGTT) at 3 months postpartum that enabled assessment of glucose tolerance, insulin sensitivity/resistance, and b-cell function (Insulin Secretion-Sensitivity Index-2 [ISSI-2]).

The postpartum OGTT identified 301 women with normal glucose tolerance (NGT) and 66 with prediabetes or diabetes. Serum prolactin in pregnancy was higher in women with postpartum NGT compared with those with postpartum prediabetes/diabetes (mean 98.2 vs. 80.2 ng/mL, P = 0.0003), whereas HPL and CMPF did not differ between the groups. On multiple linear regression analyses, antepartum prolactin was an independent determinant of postpartum ISSI-2 (b = 0.0016, t =2.96, P = 0.003). Furthermore, higher serum prolactin in pregnancy independently predicted a lower risk of postpartum prediabetes/diabetes (odds ratio 0.50, 95% CI 0.35–0.72, P = 0.0002).

Editor's comment:

A vast number of women with GDM may develop diabetes in future life. But no dependable biomarker to predict this is available with us. This study highlights that serum prolactin in pregnancy predicts postpartum beta-cell function and risk of prediabetes/diabetes. This finding needs to be verified in larger trials.

Meta-Analysis of the Impact of Statin Therapy on Low-Density Lipoprotein Cholesterol and Triglyceride Levels in Patients With Hypertriglyceridemia.

Karlson BW, Palmer MK, Nicholls SJ, Lundman P, Barter PJ. A VOYAGER Am J Cardiol. 2016;117(9):1444-1448.

This study showed that LDL Cholesterol, Triglyceride reductions in Hypertriglyceridemia vary by statin and depend of the choice and dose of statin. The study group used data from the individual patient meta-analysis of statin therapy in at-risk groups and evaluated the effects of rosuvastatin, atorvastatin, and simvastatin meta-analysis to examine LDL cholesterol and triglyceride reductions in patients with baseline triglycerides of at least 177 mg/dL. The least squares mean percentage change from baseline in LDL cholesterol and triglycerides were compared using 15800 patient exposures to rosuvastatin, atorvastatin, and simvastatin .

The researchers found that the mean reductions in LDL cholesterol varied from −26.9% to −55.5%. Significantly greater reductions in LDL cholesterol were seen for 10 mg to 40 mg rosuvastatinvs equal or double doses of atorvastatin and simvastatin (P<.05). The mean reductions in triglycerides were from −15.1% to −31.3%.

Significantly greater reductions were seen for rosuvastatin 10 mg vs atorvastatin 10 mg (P<.05) and similar reductions were noted for 20 mg to 40 mg rosuvastatinvs equal doses of atorvastatin. Significantly greater reductions were seen for rosuvastatin 20 mg to 40 mg vs equal or double doses of simvastatin (P<.05).

Editor's comment:

This is a unique study to assess the respective effects of different stations on serum triglyceride and LDL cholesterol. Rosuvastatin scores higher in this purpose. Significantly greater reductions were seen for rosuvastatin vs. atorvastatin both for 10mg and higher dosage of both. Compared with Simvastatin greater reductions were seen for rosuvastatin (P< 0.05).

Quantification of the Type 2 Diabetes Risk in Women With Gestational Diabetes: A Systematic Review and Meta-Analysis of 95,750 Women

G Rayanagoudar, AA Hashi, J Zamora, KS Khan, GA Hitman, S Thangaratinam Diabetologia 2016 Apr 13;[EPub Ahead of Print].

Gestational diabetes mellitus (GDM) identification primarily centers around improving outcomes in affected pregnancies; a secondary benefit is the opportunity for prediction of future type 2 diabetes, which would enable not only early intervention but also the possibility of prevention. At the time of diagnosis, type 2 diabetes has often been present many years, and vascular complications may already be present. In the Diabetes Prevention Program (DPP) study, the rate of development of type 2 diabetes in women with previous GDM, who had prediabetes, was cut in half in those treated with intensive lifestyle intervention or metformin, compared with untreated controls.

One of the biggest barriers to early identification and prevention in such patients is the dismally low rate of post-pregnancy testing. This systematic review reports that, in women with previous GDM, the strongest predictors of future diabetes include maternal demographics such as BMI, family history of diabetes, ethnicity and advanced maternal age as well as features of GDM including elevated fasting glucose levels, need for insulin during pregnancy, HbA1c, and early GDM diagnosis. While these risk factors are surely not independent of each other and type 2 diabetes may develop in women who had GDM even in the absence of any of these risk factors, knowledge of the risk factors should be helpful in increasing motivation of patients and caregivers to ensure testing for diabetes and prediabetes after a GDM pregnancy.

Women with gestational diabetes mellitus (GDM) are at risk of developing type 2 diabetes, but individualised risk estimates are unknown. We conducted a meta-analysis to quantify the risk of progression to type 2 diabetes for women with GDM.

The researchers systematically searched the major electronic databases with no language restrictions. Two reviewers independently extracted 2 × 2 tables for dichotomous data and the means plus SEs for continuous data. Risk ratios were calculated and pooled using a random effects model.

There were 39 relevant studies (including 95,750 women) BMI (RR 1.95 [95% CI 1.60, 2.31]), family history of diabetes (RR 1.70 [95% CI 1.47, 1.97]), non-white ethnicity (RR 1.49 [95% CI 1.14, 1.94]) and advanced maternal age (RR 1.20 [95% CI 1.09, 1.34]) were associated with future risk of type 2 diabetes. There was an increase in risk with early diagnosis of GDM (RR 2.13 [95% CI 1.52, 3.56]), raised fasting glucose (RR 3.57 [95% CI 2.98, 4.04]), increased HbA1c (RR 2.56 [95% CI 2.00, 3.17]) and use of insulin (RR 3.66 [95% CI 2.78, 4.82]). Multiparity (RR 1.23 [95% CI 1.01, 1.50]), hypertensive disorders in pregnancy (RR 1.38 [95% CI 1.32, 1.45]) and preterm delivery (RR 1.81 [95% CI 1.35, 2.43]) were associated with future diabetes. Gestational weight gain, macrosomia in the offspring or breast feeding did not increase the risk.

Editor's comment:

If followed upto 20 years after GDM about 60–70% of these women develop frank diabetes. In this cohort, data on 95,750 women were analysed for an association between gestational diabetes mellitus (GDM) and progression to type 2 diabetes. In those patients with GDM, other risk factors associated with increased future risk of type 2 diabetes included family history of diabetes, advanced maternal age, increased HbA1c, multiparity, hypertension in pregnancy and preterm delivery.

The results of this study confirm an association between GDM and future type 2 diabetes. The women with past GDM should be properly counselled about the personalised risk of progression to type 2 diabetes and motivated for regular screening.

Healthful Dietary Patterns and the Risk of Hypertension Among Women With a History of Gestational Diabetes Mellitus.

Cuilin Zhang et al A Prospective Cohort Study. HYPERTENSIONAHA. 115.06747, Published online before print April 18, 2016

Women who developed gestational diabetes mellitus represent a high-risk population for hypertension later in life. The role of diet in the progression of hypertension among this susceptible population is unknown. The researchers conducted a prospective cohort study of 3818 women with a history of gestational diabetes mellitus in the Nurses' Health Study II as part of the on-going Diabetes & Women's Health Study. These women were followed-up from 1989 to 2011.

Incident hypertension was identified through self-administered questionnaires that were validated previously by medical record review. Adherence scores for the alternative Healthy Eating Index 2010, the alternative Mediterranean diet, and the Dietary Approaches to Stop

Hypertension were computed for each participant. Cox proportional hazard models were used to evaluate the associations between dietary scores and hypertension while adjusting for major risk factors for hypertension. About 1069 incident hypertension cases during a median of 18.5 years of follow-up were detected. After adjustment for major risk factors for hypertension, including body mass index, alternative Healthy Eating Index 2010, alternative Mediterranean diet, and Dietary Approaches to Stop Hypertension scores were significantly inversely associated with the risk of hypertension; hazard ratio and 95% confidence interval comparing the extreme quartiles (highest versus lowest) were 0.76 (0.61–0.94; Pfor linear trend =0.03) for AHEI score, 0.72 (0.58–0.90; P for trend =0.01) for Dietary Approach to Stop Hypertension score, and 0.70 (0.56–0.88; P for trend =0.002) for alternative Mediterranean diet score. Adherence to a healthful dietary pattern was related to a lower subsequent risk of developing hypertension among women with a history of gestational diabetes mellitus.

Editor's comment:

Women with GDM are vulnerable for developing different features of insulin-resistance syndromes like diabetes, obesity, hypertension and coronary artery disease. This study establishes diet as a factor for developing hypertension in post GDM women and prevention is possible with healthy diet.

Low Thyroid Function Linked to Greater Type 2 Diabetes Risk.

ENDO 2016: The Endocrine Society Annual Meeting, Eckert-Norton, ENDO 2016; April 3, 2016; Boston, Massachusetts. Abstract OR33-2

This study suggests that , low and low-normal thyroid function are associated with an increased risk for type 2 diabetes .The findings, from a large population-based cohort in the Netherlands, were presented April 3 here at the annual meeting of the Endocrine Society, ENDO 2016, by Layal Chaker . Low thyroid function is associated with a higher risk of developing diabetes and also of progression from prediabetes to diabetes. This risk is also evident even among those in the low-normal range of thyroid function.

So long we have always screened for thyroid disorders in patients with type 1 diabetes, because of the autoimmune association. But there's overlap between the symptoms of hypothyroidism and type 2 diabetes. Even in Normal Range, Low Thyroid Function Predicts Diabetes .

The study included 8452 persons ,aged 45 and older without diabetes at baseline. They had a mean age of 65 years and mean body mass index (BMI) of 26.5 kg/m^2, and 58% were female. They had an average thyroid-stimulating hormone (TSH) level of 1.91 mIU/L and free thyroxine of 15.7 pmol/L, both within the expected range.

During a mean follow-up of 7.9 years, 1100 subjects developed prediabetes and 798 developed type 2 diabetes. After adjustment for sex, age, smoking, fasting serum glucose, and cohort, those in the highest tertile for TSH had a significant 1.13 times increased risk of developing type 2 diabetes compared with the lowest tertile. When limited to the 85% of subjects within the normal TSH range, there was a significant 1.24-fold elevated risk for the highest vs lowest tertile.

Higher free T4 was associated with a lower diabetes risk, with a hazard ratio of 0.96 for both the full range of measurements and those within the normal thyroid-function range. The risk of progression from prediabetes (fasting glucose 106-126 mg/dL) to type 2 diabetes (>126 mg/dL) was 1.25-fold higher comparing the lowest to the highest tertiles of TSH and 1.39 for those within the normal range (P = .002). Free T4 again showed the inverse relationship, with hazard ratios of 0.92 and 0.90 for the highest vs lowest tertiles in the full and normal ranges of thyroid-function measurements, respectively.

In absolute terms, the risk for type 2 diabetes increased from 19% to 35% as TSH rose from 0.4 to 4.0 mIU/L, while the diabetes risk dropped from 35% to 15% as free T4 increased from 11 to 25 pmol/L.

Editor's comment:

This study suggests that low and low-normal thyroid functions are associated with an increased incidence of type 2 diabetes. The probable mechanism for the association might be that thyroid hormone is important for energy expenditure and weight, so the effect might be mediated by BMI and other metabolic-syndrome components or perhaps a direct effect on beta-cell function. But it deserves further research. This is a very interesting work and I really look forward to seeing if this is true with our African-American, Latino and Asian populations."

Type 2 Diabetes Mellitus in Youth Exposed to Antipsychotics.

Galling B, Roldán A, Nielsen RE, et al. JAMA Psychiatry. 2016; doi:10.1001/jama psychiatry. 2015. 2923.

The researchers analyzedall longitudinal studies through May 4, 2015, that investigated type 2 diabetes incidences among youth taking anti psychotics for at least 3 months. They identified 13 studies with 180 105 youth exposed to antipsychotics. The participants, ranging from 2 to 24 years of age with an average age of 14 years, were tracked for an average 1.7 years and a total of 310 438 patient-years. Before adjustments, overall risk for type 2 diabetes was 5.7 per 1000 patients exposed to antipsychotics, compared with 2.6 of 1000 unexposed patients found among more than 1.34 million psychiatric controls in 7 studies.

Among nearly 300 000 healthy controls in 8 studies, the risk was 2.2 per 1000 youth. The incidence rate of type 2 diabetes was 3 per 1000 patient-years for antipsychotic exposure, 1.7 per 1000 patient-years for unexposed psychiatric controls, and 1.3 per 1000 patient-years among healthy controls.

The excess risk for type 2 diabetes, then, translated to 3 additional diagnoses for every 1000 youth receiving antipsychotics. Every 322 psychiatric patients prescribed antipsychotics would result in 1 excess type 2 diabetes case, whereas the number needed to harm compared with healthy controls was 280.

Most of the kids taking antipsychotics had been diagnosed with a disruptive behavior disorder, attention deficit/hyperactivity disorder, depression, bipolar disorder or another mood disorder. Anxiety, psychosis, autism, substance abuse disorders and tic disorders were less common.

The vast majority of youth (95%) received second-generation antipsychotics, and in the 10 studies with more specific data, risperidone comprised 42% of prescriptions, followed by quetiapinefumarate (27%), aripiprazole (17%) and olanzapine (10%).

The relevance of the findings is further underscored by the fact that type 2 diabetes mellitus is only the most severe outcome of an interplay between antipsychotic exposure and genetic and lifestyle factors that lead to obesity and insulin resistance, which in and of themselves have serious health risks, especially when starting early in life.

Editor's comment :

Use of antipsychotics increases risk for type 2 diabetes in youth. The odds of developing type 2 diabetes were twice as high in children exposed to antipsychotics as compared with those not taking the drugs, and 2.6 times higher as compared with healthy children. The risk increased with longer follow-up was greater in boys, and was particularly associated with olanzapine. While using antipsychotics in high risk group for developing diabetes, drugs which are more diabetogenic need to be avoided.

The effect of ranolazine on glycemic control in patients with type 2 diabetes treated with either glimepiride or metformin.

Pettus J, McNabb B, Eckel RH, et al. Diabetes Obes Metab. 2016; doi: 10.1111/ dom.12629.

This paper establishes that adding Ranolazine to Glimepiride Reduces HbA1c in Type 2 Diabetes. For patients with type 2 diabetes on background glimepiride therapy, but not metformin, addition of ranolazine is associated with a significant reduction in HbA1c. Jeremy Pettus et al examined the efficacy of ranolazine for glycemic control in patients with type 2 diabetes on metformin or glimepiride. They randomly assigned 431 and 442 patients to ranolazinevs placebo added to glimepiride or metformin background therapy, respectively. To correct for the metformin-ranolazine pharmacokinetic interaction, patients receiving ranolazine added to metformin had their metformin dose halved. The researchers found that, compared with placebo, the addition of ranolazine to glimepiride was associated with a 0.51% decrease from baseline in HbA1c at 12 weeks, and near doubling of the proportion of patients achieving an HbA1c of less than 7% (27.1% vs 14.1%; P=.001). There was no significant difference in the 24-week HbA1c change from baseline when ranolazine was added to metformin background therapy.

Editor's comment:

Different non-conventional drugs like proton pump inhibitors, quininine, NSAIDs etc. can lower blood sugar. When using these drugs with anti diabetics, this should be kept in mind. Ranolazine is also one of them. This analysis shows that relative to placebo, ranolazine added to glimepiride reduced HbA1c by 0.51%, while combination therapy with metformin did not significantly decrease HbA1c, though this was in the setting of reduced metformin dosing relative to those taking placebo.

Calcium channel blocker use is associated with lower fasting serum glucose among adults with diabetes from the REGARDS study.

Khodneva Y, Shalev A, Frank SJ, Carson AP, Safford MM. Diabetes Res Clin Pr. 2016; doi: 10.1016/j.diabres.2016.01.021.

For adults with diabetes, calcium channel blocker (CCB) use is associated with lower fasting serum glucose levels, according to a study published in Diabetes Research and Clinical Practice.

Yulia Khodneva et al used data from Reasons for Geographic and Racial Differences in Stroke (REGARDS) study participants enrolled between 2003 and 2007 to examine the correlations of CCB and verapamil use with fasting serum glucose. After adjustment for covariates, the correlations were examined for 4978 adults with diabetes.

The researchers found that 29.6% of participants were CCB users, of whom 3.4% were verapamil users. Compared with CCB non-users, CCB users had 5 mg/dL lower serum glucose in fully adjusted generalized linear models. Compared to CCB non-users, verapamil users had on average 10 mg/dL lower serum glucose, with considerably greater differences seen among insulin users: 24 and 37 mg/dL lower serum glucose among users of insulin and oral agents and users of insulin alone, respectively.

Editor's comment :

Existing information is against using calcium channel blockers particularly short acting ones, as first line antihypertensive agent in the presence of diabetes because of its adverse effect on beta cell. This is because of its effect through the calcium channel dependent potassium channel and resultant hyperglycaemia.

But this REGARDS study claims that CCB and in particular verapamil use was associated with lower fasting blood glucose levels among REGARDS participants with diabetes. This study, of course, needs to be verified by large studies before we change our strategy.

Folic Acid Supplements Intake in Early Pregnancy Increases Risk of Gestational Diabetes Mellitus: Evidence From a Prospective Cohort Study.

Zhu B, Ge X, Huang K, et al. Diabetes Care. 2016. doi:10.2337/dc15-2389.

Folic acid consumption in the first trimester is associated with increased risk for gestational diabetes mellitus, according to research published in Diabetes Care. Beibei Zhu, from the Anhui Medical University in Hefei, China, and colleagues used data from the prospective China-Anhui Birth Cohort Study to examine the correlation between folic acid supplement consumption and the risk for gestational diabetes.

The researchers diagnosed gestational diabetes in 12.8% of the 1938 women who had either used folic acid supplements or never used any vitamin supplements. The risk for gestational diabetes was increased in association with daily folic acid supplement consumption in the first trimester (adjusted odds ratio [OR]=2.25).

The risk for gestational diabetes was much higher for women with a prepregnancy body mass index (BMI) of 25 kg/m or greater and taking folic acid supplements daily in the first trimester vs women with a prepregnancy BMI of less than 25 kg/m and not taking folic acid supplements (OR=5.63). Women using folic acid before pregnancy alone or in the second trimester alone had no increased risk for gestational diabetes.

Editor's comment:

This study, for the first time, suggests that daily folic acid supplement consumption in early pregnancy increases the risk of gestational diabetes mellitus, and further larger cohort studies are warranted to examine this adverse effect. But women using folic acid before pregnancy alone or in the second trimester alone had no increased risk for gestational diabetes.

Till date, use of folic acid is thought to be essential in pregnancy to avoid foetal complications particularly in diabetes. No explanation is offered in this study for the causal relationship with use of folic acid. However, we should keep open minded to change our decision regarding the use of folic acid till supported by multiple larger trials.

Association of Diabetic Microvascular Complications and Parameters of Obstructive Sleep Apnea in Patients With Type 2 Diabetes

R Zhang, P Zhang, F Zhao, X Han, L Ji. Diabetes Technol. Ther. 2016 Mar 31; [EPub Ahead of Print].

Obstructive sleep apnea (OSA) is prevalent in patients with type 2 diabetes, but the influence of OSA on diabetes complications is not clear. We aimed to investigate the association of OSA with chronic diabetes complications in Chinese patients with type 2 diabetes.

In total, 880 hospitalized patients were enrolled in a multicenter, cross-sectional study that involved 12 hospitals from six cities in the People's Republic of China.

Overnight sleep monitoring with a portable monitor was used to record respiratory parameters, including the apnea-hypopnea index (AHI), the oxygen desaturation index (ODI), the oxygen saturation (SPO2), and the cumulative time of SPO2 below 90% or 85% (CT90% and CT85%, respectively). Chronic diabetes complications were recorded from medical charts.

CT90% was independently associated with diabetic nephropathy (DN) after adjusting for age, sex, diabetes duration, glycosylated hemoglobin, body mass index, hypertension, and the use of angiotensin converting enzyme inhibitor/angiotensin receptor blocker drugs within 1 week. The associated parameters increased from two (the average SPO2 and CT90%) to three (ODI, the lowest SPO2, and CT85%) when the severity of DN increased from micro albuminuria to renal insufficiency. The estimated glomerular filtration rate was independently correlated with ODI ($\beta = -0.172$, $P = 0.029$) and the lowest SPO2 ($\beta = 0.354$, $P = 0.004$) after adjustments. The lowest SPO2 was associated with proliferative diabetic retinopathy by univariate logistic regression but was not significant in multivariate regression after adjustment.

Editor's comment:

This study is from China, a multi centre, cross-sectional study of 880 hospitalised patients. This study shows that, in overnight in-hospital sleep monitoring, the cumulative time of SPO2 below 90% was independently associated with diabetic nephropathy and the oxygen desaturation index was independently associated with the estimated glomerular filtration rate. The nocturnal hypoxemia in obstructive apnea in presence of diabetes was associated with diabetic nephropathy and affected the renal function of patients with type 2 diabetes. The parameters of hypoxemia may more sensitively reflect the association of OSA and diabetic microvascular complications than apnea-hypopnea index.

Long-Term Benefits of Intensive Glucose Control for Preventing End-Stage Kidney Disease: ADVANCE-ON.

MG Wong, V Perkovic, J Chalmers, M Woodward, Q Li, ME Cooper, P Hamet, S Harrap, S Heller, S MacMahon, G Mancia, M Marre, D Matthews, B Neal, N Poulter, A Rodgers, B Williams, S Zoungas. Diabetes Care 2016 Mar 22; [EPub Ahead of Print].

Intensive glucose control for preventing end-stage kidney disease has been studied in this paper. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Released Controlled Evaluation (ADVANCE) trial reported that intensive glucose control prevents end-stage kidney disease (ESKD) in patients with type 2 diabetes, but uncertainty about the balance between risks and benefits exists. The study group examined the long-term effects of intensive glucose control on risk of ESKD and other outcomes.

Survivors, previously randomized to intensive or standard glucose control, participated in post-trial follow-up. ESKD, defined as the need for dialysis or kidney transplantation, or death due to kidney disease, was documented overall and by baseline CKD stage, along with hypoglycemic episodes, major cardiovascular events, and death from other causes.

A total of 8,494 ADVANCE participants were followed for a median of 5.4 additional years. In-trial HbA1c differences disappeared by the first post-trial visit. The in-trial reductions in the risk of ESKD (7 vs. 20 events, hazard ratio [HR] 0.35, $P = 0.02$) persisted after 9.9 years of overall follow-up (29 vs. 53 events, HR 0.54, $P < 0.01$). These effects were greater in earlier-stage CKD ($P = 0.04$) and at lower baseline systolic blood pressure levels ($P = 0.01$). The effects of glucose lowering on the risks of death, cardiovascular death, or major cardiovascular events did not differ by levels of kidney function ($P > 0.26$).

Intensive glucose control was associated with a long-term reduction in ESKD, without evidence of any increased risk of cardiovascular events or death. These benefits were greater with preserved kidney function and with well-controlled blood pressure.

Editor's comment:

This study is a long-term follow-up of patients enrolled in the ADVANCE trial. Out of 8494 patients with type 2 diabetes mellitus followed for an average of 9.9 years, intense glucose control was associated with a reduction in end-stage kidney disease (ESKD) compared with standard glucose control. The benefits of intense glucose control were seen to be better for patients with early-stage chronic kidney disease and for patients with lower baseline systolic blood pressure. Study results indicate that intensive glucose control is associated with a long-term reduction in ESKD.

Pre-Pregnancy Adverse Lipid Profile and Subsequent Risk of Gestational Diabetes.

ES Han, RM Krauss, F Xu, SB Sridhar, A Ferrara, CP Quesenberry, MM Hedderson .J. Clin. Endocrinol. Metab. 2016 Apr 05; [EPub Ahead of Print].

In this study patients who underwent blood testing before becoming pregnant, 254 women who developed gestational diabetes mellitus (GDM) were each matched to two controls matched for year of blood draw, age at baseline, age at pregnancy, and number of intervening pregnancies. Adjusting for confounding variables, women in the low quartiles of LDL peak diameter and HDL were at increased odds of GDM compared with women in the high quartiles. Women in the high quartiles of small and very small LDL sub-fractions were at increased odds of GDM compared with women in the low quartiles.

Based on the findings of this study, pre-pregnancy lipid profiles may predict the development of GDM. Lower LDL peak diameter and a predominance of small, dense LDL are associated with type 2 diabetes, but it is unclear whether they are a risk factor for gestational diabetes mellitus (GDM).

The study aimed at evaluating whether pre-pregnancy lipid profile predicts development of GDM during pregnancy. A nested case-control study among women who participated in a multiphasic health exam where blood was collected and stored between 1984 and 1996 and then had a subsequent pregnancy between 1984 and 2009. Cases were 254 women who developed GDM. Two controls were selected for each case and matched for year of blood draw, age at baseline, age at pregnancy, and number of intervening pregnancies.

The main outcome measures were ,pre-pregnancy LDL peak diameter and pre-pregnancy lipid sub fraction concentrations grouped according to size, and odds of developing GDM.

Women in the lowest quartiles of LDL peak diameter and HDL had increased odds of GDM compared with women in the highest quartiles [OR (95% CI): 2.60 (1.37-4.94) and 1.98 (1.01-3.86), respectively], in multivariable adjusted models. Being in the highest quartile of small and very small LDL sub-fractions also increased the odds of GDM [2.61 (1.35-5.03) and 2.44 (1.22-4.85), respectively].

Editor's comment:

The risk factors for developing GDM are many. This study establishes the role of atherogenic lipid profile existing from pre-pregnancy stage. Explanation may be the presence of insulin resistance.

Lower LDL peak diameter size and HDL levels and higher levels of small and very small LDL sub fraction groups were present years before pregnancy in women who developed GDM. A pre-pregnancy atherogenic lipid profile may help to identify women at risk of GDM to target for prevention.

Long-Term Maintenance of Efficacy of Dapagliflozin in Patients With Type 2 Diabetes Mellitus and Cardiovascular Disease

LA Leiter, WT Cefalu, TW de Bruin, J Xu, S Parikh, E Johnsson, I Gause-Nilsson .Diabetes Obes Metab 2016 Mar 24; [EPub Ahead of Print].

The aim of this study was to evaluate the long-term efficacy, safety and tolerability of dapagliflozin versus placebo added to usual care in patients with type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD).

Data were pooled from two phase 3 studies (NCT01031680, NCT01042977) in high-risk patients (N=1887) with T2DM and CVD treated with dapagliflozin (10 mg/day) or placebo. Patients completing the double-blind treatment studies (24 weeks) entered one or two sequential double-blind, long-term (LT) extensions of 28 (LT1; N=1649) and 52 (LT2; N=568) weeks.

Baseline and CVD characteristics were similar between groups. Patients entering LT1 and LT2 on dapagliflozin maintained a greater mean reduction in glycated haemoglobin (HbA1c) versus placebo at 52 (LT1: -0.58% [95% CI: -0.68, -0.49]) and 104 (LT2: -0.35% [95% CI: -0.59, -0.12]) weeks. Mean body weight and systolic blood pressure (SBP) reductions versus placebo were maintained in patients entering LT1 (52 weeks: -2.23 kg, -3.25 mmHg) and LT2 (104 weeks: -3.16 kg, -2.03 mmHg).

Patients on dapagliflozin had a better three-item composite endpoint of clinical benefit (glycaemia, weight and SBP) compared with placebo at week 24 (LT1: 10.1% vs. 1.1%) through to 104 weeks (LT2: 6.7% vs. 1.4%). Genital and urinary tract infections were more frequent with dapagliflozin than with placebo. Events of hypoglycaemia, renal impairment/failure and volume depletion were similar between groups.

Editor's comment:

This pooled analysis of data was done from two phase III studies to evaluate the long-term efficacy, safety and tolerability of dapagliflozin in high-risk patients with type 2 diabetes and cardiovascular disease. Patients were treated with dapagliflozin (10 mg/day) and compared with placebo. During weeks 24 to 104, patients on dapagliflozin had a better three-item composite endpoint (HbA1c, body weight and systolic blood pressure) of clinical benefit. The frequency of hypoglycaemia, renal impairment/failure and volume depletion was similar between groups; the frequency of genital and urinary tract infections was greater with dapagliflozin. In this pooled analysis of patients with type 2 diabetes and high cardiovascular risk, HbA1c, systolic blood pressure and weight reductions were maintained over 2 years with dapagliflozin.

This long-term efficacy of dapagliflozin to maintain reductions in HbA1c, SBP and body weight over 2 years, and its tolerability profile, make dapagliflozin an appropriate option in high-risk patients with T2DM, obesity and CVD.

Risk of Epilepsy in Type 1 Diabetes Mellitus: A Population-Based Cohort Study

IC Chou, CH Wang, WD Lin, FJ Tsai, CC Lin, CH Kao. Diabetologia 2016 Mar 31; [EPub Ahead of Print].

Type 1 diabetes mellitus is a major public health problem of increasing global concern, with potential neurological complications. A possible association exists between type 1 diabetes and subsequent epilepsy. This study evaluated the relationship between type 1 diabetes and epilepsy in Taiwan.

Claims data from the Taiwan National Health Insurance Research Database were used to conduct retrospective cohort analyses. The study cohort contained 2568 patients with type 1 diabetes, each of whom was frequency-matched by sex, urbanisation of residence area and index year with ten patients without type 1 diabetes. Cox proportional

hazard regression analysis was conducted to estimate the effects of type 1 diabetes on epilepsy risk.

In patients with type 1 diabetes, the risk of developing epilepsy was significantly higher than that in patients without type 1 diabetes ($p < 0.0001$ for logrank test). After adjustment for potential confounders, the type 1 diabetes cohort was 2.84 times as likely to develop epilepsy than the control cohort was (HR 2.84 [95% CI 2.11, 3.83]).

Editor's comment:

In this analysis of data from the Taiwan National Health Insurance Research Database, 2568 patients with type 1 diabetes were compared with patients without type 1 diabetes. With and without adjusting for potential confounding variables, patients with type 1 diabetes were more likely to develop epilepsy than patients without type 1 diabetes.

The effect of insulin resistance and hyperglycaemia or hypoglycaemia on the brain is not clearly understood. Patients with type 1 diabetes are at an increased risk of developing epilepsy. Metabolic abnormalities of type 1 diabetes, such as hyperglycaemia and hypoglycaemia, may have a damaging effect on the central nervous system and can be associated with significant long-term neurological sequelae. The causative factors between type 1 diabetes and the increased risk of epilepsy require further investigation.

"The world is a book and those who do not travel read only one page."

— Augustine of Hippo