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JOURNAL WATCH

Impact of Gestational Diabetes Mellitus and High Maternal Weight on the Development of Diabetes, Hypertension and Cardiovascular Disease: A Population-Level Analysis.

Diabet. Med. 2015 Feb 01;32(2)164-173, P Kaul, A Savu, KA Nerenberg, LE Donovan, CL Chik, EA Ryan, JA Johnson

Editor's Comment

The risk for development of T2DM in patients after gestational diabetes (GDM) is well established. But the researchers here studied the impact of high maternal weight on further cardiovascular disease in a population of more than 240,000 Canadian singleton deliveries over 10 years.T2DM developed in 36% of overweight patients who had GDM, 18.8% of patients who only had GDM, and 4.8% of patients who were only overweight. A similar pattern was seen in the development of hypertension and cardiovascular disease in these groups. High maternal weight and GDM were independent risk factors for hypertension and cardiovascular disease, but high maternal weight compared to GDM appears to be stronger.

Women with singleton deliveries between April 1999 and March 2010 in Alberta, Canada, were categorized according to pre-pregnancy weight (overweight e" 91 kg) and GDM status. Obstetric and neonatal outcomes, as well as the long-term incidence of maternal diabetes, hypertension and cardiovascular disease were examined.

Out of the 240 083 women, 213 765 (89%) had no GDM and were not overweight (reference group), 17 587 (7.3%) were overweight only, 7332 (3%) had GDM only and 1399 (0.6%) had GDM and were overweight. Significant differences in Caesarean section rates, induction rates and birth-weight were observed across the four groups. During a median follow-up of 5.3 years, diabetes incidence was 36% in the GDM and overweight, 18.8% in the GDM only, 4.8% in the overweight only and 1.1% in the reference group. With respect to hypertension and cardiovascular disease, the GDM and overweight group had the highest rates (26.8% and 3.1%, respectively) and the reference group had the lowest rates (5.8% and 1.0%, respectively). However, rates were similar in the GDM only (14.9% and 1.9%, respectively) and overweight only groups (14.9% and 1.5%, respectively).

Not surprisingly, the presence of both high maternal weight and GDM compounds the risk of developing diabetes. However, the association between overweight alone and GDM alone and hypertension and cardiovascular disease appears similar suggesting a need for effective interventions to manage both these conditions to improve the health of these patients.

Guideline Treatment Results in Regression of Atherosclerosis in Type 2 Diabetes Mellitus

Diab Vasc Dis Res 2015 Mar 01;12(2)126-132, AC Strang, DF van Wijk, HJ Mutsaerts, ES Stroes, AJ Nederveen, JI Rotmans, TJ Rabelink, FM Box

Editor's Comment

In this study, the researchers compared the carotid artery wall of 30 patients with type 2 diabetes with that of 29 controls after stroke or myocardial infarction who were receiving treatment according to the cardiovascular risk–management guidelines. Carotid artery wall dimensions were significantly decreased in patients with type 2 diabetes and stabilized in controls. This study suggest that optimal cardiovascular disease prevention is not only beneficial, but possible and necessary especially for patients with type 2 diabetes.

Efficacy of guideline cardiovascular disease prevention regimens may differ between patients with or without type 2 diabetes mellitus. The researchers compared change in carotid artery wall dimensions in type 2 diabetes mellitus and non-type 2 diabetes mellitus patients with a history of a major cardiovascular disease event, using magnetic resonance imaging.

Thirty type 2 diabetes mellitus patients and 29 age and sexmatched non-diabetes mellitus patients with a history of stroke or myocardial infarction and a carotid artery stenosis (15%-70%) were included. In all patients, treatment was according to cardiovascular risk management guidelines. At baseline and follow-up, carotid artery vessel wall dimensions were measured using 1.5 T magnetic resonance imaging.

After a follow up for 2 years, total wall volume of the carotid artery in type 2 diabetes mellitus patients decreased by 9.6% ($p = 0.016$). But,stabilization rather than regression of carotid artery wall dimensions was observed in non-diabetes mellitus patients over a 2 year period. Body mass index seen as a predictor of total wall volume decrease.

Guideline treatment arrests atherogenesis in non-diabetes mellitus patients and even decreases vessel wall dimensions in type 2 diabetes mellitus patients. Baseline body mass index predicts cardiovascular disease prevention efficacy expressed as decrease in total wall volume. These data emphasize the importance of optimal cardiovascular-prevention, particularly in diabetes patients with a high body mass index.

Earlier Menarche is Associated with Fatty Liver and Abdominal Ectopic Fat Obesity.

Obesity; 2015 Feb 01; 23 (2)468-474; NT Mueller, MA Pereira, EW Demerath, et al

Editor's Comment

Researchers evaluated 1214 women over a duration of 25years to determine the association of menarche with non-alcoholic fatty liver disease (NAFLD) and ectopic adiposity. NAFLD and ectopic adiposity were associated with earlier menarche, independent of body mass index at baseline. The study suggest that weight maintenance should be a focus in care for women during young adulthood through midlife, particularly for those who had early menarche.

In this study, the hypothesis that earlier menarche is associated with higher non-alcoholic fatty liver disease (NAFLD) and ectopic adiposity, independent of young adult body mass index (BMI), was tested.

The data from 1,214 black and white women in the Coronary Artery Risk Development in Young Adults (CARDIA) study who reliably reported menarche age at exam years 0 and 2, who had multiple-slice abdominal

computed tomography (CT) at exam year 25, and who had no known liver disease or secondary causes of steatosis were included. Women were aged 18-30 at year 0 and 43-55 at year 25. Liver attenuation, visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and inter-muscular adipose tissue (IMAT) were derived from CT. NAFLD was defined as liver attenuation less than 51 Hounsfield units.

One-year earlier menarche was associated with higher NAFLD (RR = 1.15; 95% CI: 1.07, 1.24), and VAT (6.7 cc; 95% CI: 4.3, 9.0 cc), IMAT (1.0 cc; 95% CI: 0.6, 1.4 cc), and SAT (19.6 cc; 95% CI: 13.2, 26.0 cc) after confounder adjustment. Associations remained significant ($P < 0.05$) after further adjustment for year 0 BMI. Only VAT remained significant ($P = 0.047$) after adjustment for weight gain between years 0 and 25.

Earlier menarche is positively associated with NAFLD and ectopic fat independent of confounders and young adult BMI. Weight gain between young adulthood and midlife explains some of this association.

Effects of Higher-Intensity Exercise on Weight Loss and Waist Circumference

Robert Ross, PhD; Robert Hudson, MD, PhD†; Paula J. Stotz, MSc; and Miu Lam, PhDAnn Intern Med. 2015;162(5): 325-334.

Exercise reduces obesity and related glucose tolerance, but whether increasing exercise intensity offers additional benefit at fixed exercise amounts is unknown.

This study determined the separate effects of exercise amount and intensity on abdominal obesity and glucose tolerance in a 24-week, single-center, parallel-group trial from 2009 to 2013. (ClinicalTrials.gov: NCT00955071) in a cohort of 300 abdominally obese adults.

Intervention: Control (no exercise) (n = 75) or 5 weekly sessions of low-amount, low-intensity exercise (LALI) (180 and 300 kcal/session for women and men, respectively, at 50% of maximum oxygen consumption [Vo2peak]) (n = 73); high-amount, low-intensity exercise (HALI) (360 and 600 kcal/session, respectively, at 50% of Vo2peak) (n = 76); or high-amount, high-intensity exercise (HAHI) (360 and 600 kcal/session, respectively, at 75% of Vo2peak) (n = 76). Daily unsupervised physical activity and sedentary time were measured by accelerometer.

Measurements were done with waist circumference and 2-hour glucose level (primary outcomes) and cardiorespiratory fitness and measures of insulin action (secondary measurements).

217 participants (72.3%) completed the intervention. Mean exercise time in minutes per session was 31 (SD, 4.4) for LALI, 58 (SD, 7.6) for HALI, and 40 (SD, 6.2) for HAHI. Daily unsupervised physical activity and sedentary time did not change in any exercise group versus control ($P > 0.33$). After adjustment for age and sex in a linear mixed model, reductions in waist circumference were greater in the LALI (“3.9 cm [95% CI, “5.6 to “2.3 cm]; $P < 0.001$), HALI (“4.6 cm [CI, “6.2 to “3.0 cm]; $P < 0.001$), and HAHI (“4.6 cm [CI, “6.3 to “2.9 cm]; $P < 0.001$) groups than the control group but did not differ among the exercise groups ($P > 0.43$). After adjustment for covariates, reductions in 2-hour glucose level were greater in the HAHI group (“0.7 mmol/L [“12.5 mg/dL] [CI, “1.3 to “0.1 mmol/L {“23.5 to “1.5 mg/dL}]; $P = 0.027$) than the control group but did not differ for the LALI or HALI group versus the control group ($P > 0.159$). Weight loss was greater in all exercise groups than the control group ($P < 0.001$); however, reduction in body weight did not differ among the exercise groups ($P > 0.182$).

Fixed amounts of exercise independent of exercise intensity resulted in similar reductions in abdominal obesity. Reduction in 2-hour glucose level was restricted to high-intensity exercise.

Vildagliptin Lowers Hepatic Triglyceride Levels But Does Not Affect Body Weight or Peripheral Insulin Sensitivity

Mavin Macauley et al .The Journal of Clinical Endocrinology & Metabolism, online February 9.

Editor's Comment

This study demonstrates for the first time that DPP4 (dipeptidyl peptidase-4) inhibition can bring about clinically useful decreases in liver triglyceride levels associated with both a fall in plasma ALT (alanine aminotransferase) and plasma glucose. This study is interesting in the sense that extraglycemic effect of DPP4 inhibitors like amelioration of hepatic fat accumulation in the liver is highlighted here. If larger trials favour this study, then gliptins may be of choice in cases of type 2 diabetes with NAFLD.

The researchers studied 44 men and women who had been diagnosed with type 2 diabetes mellitus at least six months before enrolment. They were randomly assigned to take either 50 mg of vildagliptin or placebo twice a day for six months.

All the patients were only on stable metformin therapy. Their hemoglobin A1c (HbA1c) was 7.6% or lower and their body mass index (BMI) was between 22 and 38 kg/m2. Among participants who received vildagliptin, the mean fasting liver triglyceride content decreased by 27% (from 7.3% at baseline to 5.3%), while the placebo group showed no change.

The between-group difference in the change from baseline was significant (p=0.013), and the mean fasting plasma glucose concentration decreased by 1.0 mmol/L with vildagliptin compared with placebo (p=0.018). The correlation between these decrements and liver triglyceride in the vildagliptin group was significant at three and six months.

In the vildagliptin group, plasma ALT fell from 27.2 to 20.3 IU/l (p=0.0007), correlating with the drop in liver triglyceride (r=0.83; p<0.0001).Insulin sensitivity during the euglycemic clamp was similar in both groups at baseline and did not change significantly over the study. In the vildagliptin and placebo groups respectively, mean body weight decreased by 1.6 kg compared with 0.4 kg (p=0.08).

Metformin Prevents Type 2 Diabetes, When Followed-up After Gestational Diabetes

Vanita R Aroda et al.J Clin Endocrinol Metab. Published online February 23, 2015.

Editor's Comment

Women with Gestational Diabetes are at Higher Risk for Type 2 Diabetes.Both lifestyle intervention and use of the drug metformin reduced the risk for type 2 diabetes among women with a history of gestational diabetes mellitus (GDM) in a 10-year study.But metformin failed to affect diabetes risk among those without a history of GDM, according to this new analysis of the Diabetes Prevention Program Outcomes Study (DPPOS).This is probably the longest-term look at progression to [type 2] diabetes for women with a history of gestational diabetes. It appears thatmetformin is a viable alternative to lifestyle intervention among women with a history of gestational diabetes.

The results confirm that pregnancy operates like a "stress test for the body," signaling a high probability of progression to diabetes, she said. It's important to assess whether a woman had gestational diabetes. People tend to forget about it after the baby is delivered, but long after the baby is delivered the risk is quite high, and this study shows one can do something about it.

The women studied were part of the DPPOS, which is a long-term follow-up of the 3-year Diabetes Prevention Program (DPP), which randomized overweight or obese

people at high risk for type 2 diabetes to intensive lifestyle change that included a goal of 7% weight loss and 150 minutes or more per week of moderate-intensity physical exercise; 850 mg of metformin twice daily; or placebo.

There were 3234 participants originally enrolled, with a mean body mass index (BMI) of 34 kg/m2. Of DPP participants, 68% were women and 45% were from ethnic minority groups.

The most recent results from the overall DPPOS/DPP study were reported at the American Diabetes Association meeting last year, showing that intensive lifestyle change or giving metformin can reduce or delay the development of type 2 diabetes for as long as 15 years, in some cases. These data also hinted at a stronger effect of both the lifestyle intervention and metformin compared with placebo in women with prior gestational diabetes.

This new analysis specifically examined 350 women with a history of GDM and 1416 women with previous live births, but no gestational diabetes from DPPOS.Women with a history of GDM assigned to the placebo group had a 48% higher risk of progressing to type 2 diabetes than women without a history of gestational diabetes.

Among those who had had gestational diabetes, both intensive lifestyle intervention and metformin reduced progression to diabetes compared with placebo, by 35% and 40% respectively.

However, among women with no prior GDM, metformin had no impact while intensive lifestyle intervention reduced progression to diabetes by 30%, although this latter finding differed by age.

Among the 325 women 25 to 44 years old without a history of GDM, neither intensive lifestyle intervention nor metformin reduced progression to diabetes.But women 60 and older who'd not had gestational diabetes saw a 41% reduction in progression to diabetes with intensive lifestyle, although metformin did not have any effect.

The finding that metformin fails to halt diabetes progression in women without a history of gestational diabetes is unique, as the drug also effectively prevents progression to diabetes in young men.

Although the greatest risk for type 2 diabetes was in the first 5 years after pregnancy, the chance of diabetes developing did not disappear after this period. The risk sustained after 10 years and beyond.

In a number-needed-to-treat analysis, the study found seven women with GDM would need to receive metformin to prevent one case of type 2 diabetes within 10 years, and 11 women with GDM would need to participate in intensive lifestyle modification to prevent one case of diabetes in 10 years.

Among women who had given birth with impaired glucose tolerance but no gestational diabetes, 10 women would need to participate in intensive lifestyle modification to prevent one diabetes case.The results of this longer-term study are consistent with the initial DPP results and confirm the importance of metformin.

High-Energy Breakfast Improved Blood Glucose Control in Type 2 Diabetes.

Jakubowicz D et al. Diabetologia. 2015;doi:10.1007/s00125-015-3524-9.

Editor's Comment

A small study published in Diabetologia show that the patients with type 2 diabetes, consuming a high-energy breakfast and reduced-energy dinner led to better blood glucose control when compared with those who took a high-energy dinner and reduced-energy breakfast.These observations indicate that a change in meal timing influences the overall daily rhythm of post-meal insulin and incretin and results in a substantial reduction in the daily post-meal glucose levels. The mechanism of better glucose tolerance after high-energy breakfast than after an identical dinner may be in part the result of clock regulation that triggers higher beta cell responsiveness and insulin secretion in the morning, and both a lower rate of breakdown of insulin by the liver and the increase in insulin-mediated muscle glucose uptake in the morning.

This randomized, open label, crossover study enrolled 22 patients with type 2 diabetes of less than 10 years duration. Patient age were from 30 to 70 years; BMI from 22 to 35; and HbA1c from 7% to 9%. All were also being treated with metformin and/or diet.A total of 18 completed the study and were included in the analysis.

The patients were randomly assigned to a diet that included a high-energy breakfast and a reduced-energy

dinner (Bdiet) or a diet that included a reduced-energy breakfast and a high-energy dinner (Ddiet) for 7 days. The Bdiet was comprised of a 2,946-kJ breakfast, a 2,523-kJ lunch and an 858-kJ dinner, whereas the Ddiet involved an 858-kJ breakfast, a 2,523-kJ lunch and a 2,946-kJ dinner.

Postprandial levels of plasma glucose, insulin, C-peptide and intact and total glucagon-like peptide-1 (iGLP-1 and tGLP-1, respectively) were evaluated.According to results, during the day, the area under the curve (AUC) for glucose among patients on the Bdiet was 20% lower, whereas levels of insulin, C-peptide and tGLP-1 levels were 20% higher when compared with the Ddiet group.

Three hours after eating, the AUC peak for glucose was 24% lower and insulin AUC 11% higher with the Bdiet. Also higher in the Bdiet group at this time were levels of tGLP-1 (+30%) and iGLP-1 (+16%).

In addition, despite lunches containing the same total energy and calories in both groups, lunch in the Bdiet group resulted in lower glucose by 21% to 25% and higher insulin by 23%. Thus, recommending a higher energy load at breakfast, when beta cell responsiveness and insulin-mediated muscle glucose uptake are at optimal levels, seems an adequate strategy to decrease post-meal glucose spikes in patients with type 2 diabetes.

Possible Effects of Glimepiride beyond Glycemic Control in Patients with Type 2 Diabetes: A Preliminary Report

Ikuko Nakamura et al.Cardiovascular Diabetology 2014, 13:15

Editor's Comment

Diabetes itself does not do much harm. Major problems arise from its complications.We expect that optimal antidiabetic drugs must exert beneficial effects that can help to prevent diabetic complications, in addition to providing good glycemic control.

Glimepiride is a second-generation sulfonylurea that stimulates pancreatic â cells to release insulin. This agent mainly stimulates insulin secretion, but has also been shown to have additional extra-pancreatic effects. The aim of this study was to elucidate the beneficial effects of glimepiride on cardiovascular system related biomarkers in diabetic patients. Glimepiride may have potent anti-oxidative, anti-inflammatory and angiogenic properties and it may potentially repair tissue damage by decreasing the levels of toxic AGE and increasing colony-stimulating factors. If all these effects are substantial, glimepiride should be considered as choice of sulfonylurea.

The purpose of this study was to elucidate the effects of glimepiride on the levels of biomarkersrelated to cardiovascular regulation in patients with type 2 diabetes mellitus.

Thirty-four patients with type 2 diabetes received glimepiride for 24 weeks. Significantdecreases in the levels of glyceraldehyde-derived advanced glycation end products, (glycer-AGE: toxic AGE), eotaxinand fibroblast growth factor (FGF)-2 were recognized after the administration of glimepiride.

Moreover, there weretrends for there to be increases in the levels of granulocyte-colony stimulating factor (G-CSF) and granulocytemacrophage-colony stimulating factor (GM-CSF), and decreases in the levels of fractalkine, soluble CD40 ligand (sCD40L), macrophage inflammatory protein (MIP)-β, vascular endothelial growth factor (VEGF) and soluble receptorfor AGE (sRAGE).