Diabetes Management

Our panel of experts highlight the most important research articles across the spectrum of topics relevant to the field of diabetes management

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Delahanty LM, Pan Q, Jablonski KA *et al.* Effects of weight loss, weight cycling, and weight loss maintenance on diabetes incidence and change in cardiometabolic traits in the diabetes prevention program. *Diabetes Care* 37(10), 2738–2745 (2014).

Obesity is an established risk factor for Type 2 diabetes. Biopsychosocial factors often influence a person's ability to follow through with weight loss goals and can be considerably influenced by cultural, emotional and environmental stresses. Difficulty with consistent follow through can result in body weight fluctuation. Few studies have considered the dynamic nature of changes in body weight in relation to diabetes and cardiometabolic risk. This study by Delahanty *et al.* explores the relationship between weight fluctuation, incidence of diabetes, and improvement in cardio-metabolic risk factors over 2 years. After excluding 79 participants of less than 2 years participation or missing measurement, the investigators analyzed 1000 participants from the lifestyle intervention arm of Diabetes Prevention Program study. The study examined baseline weight, changes of body weight over different time intervals, and a number of ≥5-pound weight fluctuations (weight cycling). Patients in the Diabetes Prevention Program lifestyle intervention arm had mean weight loss of 6.84 kg at 6 months and sustained a mean weight loss of 5.39 kg at 2 years. There was a modest weight regain of 0.61 kg over the following 18 months, and a rapid weight regain of 1.38 kg between 18 and 24 months. The mean number of 5-pound weight cycles was 1.45. Weight cycling was positively associated with diabetes when adjusted by baseline weight (HR: 1.22; 95% CI: 1.02–1.48) or by 2-year weight loss (HR: 1.22; 95% CI: 1.02–1.47) respectively but not for cardio-metabolic traits. However, weight cycling was not associated with diabetes when the model adjusted by both baseline weight and 2-year weight loss (HR: 1.11; 95% CI: 0.91–1.35). Strengths of the study include the high quality of data, the ethnically diverse sample with impaired glucose tolerance, the systematic implementation of the weight loss intervention, and the direct measurement of weight (rather than from self-report). However, there were no measurements of body fat distribution, and weight as a proxy for change in adiposity may lack precision. The most important limitation in interpreting the implications of the results is that no significance to weight cycling was observed when the model was adjusted by both baseline weight and 2-year weight loss. Thus, this paper generates some very interesting hypothesis around the clinical role of weight cycling but may not be sufficiently robust to change clinical care.

– Written by Hong Xiao & Richard W Grant

Booth H, Khan O, Prevost T *et al.* Incidence of Type 2 diabetes after bariatric surgery: population based matched cohort study. *Lancet Diabetes Endocrinol.* 2(12), 963–968 (2014).

Obesity-related diabetes is an increasing worldwide health problem. Lifestyle changes, while

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effective in the early stages of intervention, are difficult for many patients to adopt and sustain. More aggressive interventions may be necessary to address and curb this epidemic. The effective use of bariatric surgical procedures to prevent Type 2 diabetes in obese people has not been well defined. This study investigated the benefits of bariatric surgery as a treatment for prevention of diabetes in obese individuals. Booth *et al.* conducted a population-based matched cohort study based on the information from UK Clinical Practice Research Datalink. They identified 2167 obese adults without diabetes who had bariatric surgery from 2002 to 2014 and matched them with 2167 controls (by BMI, age, sex, index year and HbA1c) who had not had surgery and identified new diagnoses of diabetes. There were three types of surgery procedures examined: laparoscopic gastric banding, gastric bypass and sleeve gastrectomy. The study found that over a 7-year follow-up, 4.3% of bariatric surgery patients and 16.2% of matched controls developed diabetes. The adjusted hazard ratio for developing diabetes was 0.2 (95% CI: 0.13–0.30). The study results confirmed that bariatric surgery is associated with reduced incidence of diabetes in obese patients. The strengths of the study included the large population-based sample, long term follow-up, and well documented clinical data in primary care setting. Because access to bariatric surgery is severely limited in the UK, people receiving the surgery were not representative of the general obese population. This selection pressure may have introduced bias. For example, patients who were able to obtain bariatric surgery may have been more motivated and this trait may also be related to their risk of developing diabetes (e.g., more motivated patients may also exercise more or eat better). Nonetheless, the five-fold decreased diabetes incidence is not likely to be due to solely to bias or confounding. The results of this study strongly support the value of bariatric surgery for obese patients at risk of diabetes.

– Written by Hong Xiao & Richard W Grant

Pritchard N, Edwards K, Russell AW, Perkins BA, Malik RA, Efron N. Corneal confocal microscopy predicts 4-year incident peripheral neuropathy in Type 1 diabetes. *Diabetes care* doi:10.2337/dc14-2114 (2015) (Epub ahead of print).

Over the last decade, the potential of using the novel non-invasive ophthalmic technique of corneal confocal microscopy (CCM) as a diagnostic tool for assessing diabetic peripheral neuropathy (DPN) has been established. Pritchard *et al.* evaluated the capacity of CCM, as well as conventional neuropathy measures to predict the development of DPN. In total, 90 patients with Type 1 diabetes who did not have DPN as defined by the gold standard Toronto Criteria underwent assessments of neuropathy at baseline and after 4 years. This study reports that 18% of participants developed DPN after 4 years. The factors that were found to predict the future onset of DPN included, longer duration of diabetes, higher triglyceride levels, signs of retinopathy and nephropathy, deficits in neuropathy disability score, impaired cold and warm sensation and pain thresholds, higher vibration perception threshold, slower sural and peroneal nerve conduction velocity and CCM. CCM was able to predict 4-year incidence of DPN with 63% sensitivity and 74% specificity for a corneal nerve fibre length cut-off of 14.1 mm/mm^2. The authors then assessed combinations of the neuropathy measures and found that this did not increase predictive capability compared to single measures. These findings further extend the diagnostic capability of CCM as a tool to evaluate DPN.

– Written by Shazli Azmi & Maryam Ferdousi

Tone A, Nguyen S, Devemy F *et al.* Six-week versus twelve-week antibiotic therapy for nonsurgically treated diabetic foot osteomyelitis: a multicenter open-label controlled randomized study. *Diabetes Care* 38, 302–307 (2015).

Current international guidelines suggest the use of antibiotic therapy for at least 3 months for the treatment of osteomyelitis in diabetic foot wounds when treated non-surgically. However there are issues with antimicrobial resistance and drug-related adverse effects with long duration treatment. The authors conducted a prospective randomized trial comparing 6- versus 12-week duration of antibiotic treatment in patients with diabetic foot osteomyelitis treated non-surgically with rifampicin and fluoroquinolone combinations being used as first-line therapy. In total 40 patients were randomized from 5 centers with 20 being treated for 6 weeks and 20 for 12 weeks. The primary outcome measure was the proportion of patients who achieved remission which was defined as absence of any local or systemic sign

of infection, stabilized or improved x-ray abnormalities at 1 year and complete sustained healing of the wound as well as no relapsing infection in the follow-up period of 12 months. The secondary outcome was adverse events related to antibiotic use. At 12 months, remission was obtained in 65% of patients with no significant differences between those treated for 6 or 12 weeks (12/20 vs 14/20; p = 0.5). In the remaining patients with failure of treatments this was due to a non-healing wound, relapsing osteomyelitis and worsening radiological outcome. The strengths of this study were that all patients had x-rays to establish diagnosis and bone biopsies to guide antibiotic therapy. The weaknesses of the study were the small sample size and the limited duration of follow-up. The authors suggest that 6 weeks of antibiotic therapy for patients with diabetic foot osteomyelitis may be sufficient for patients and associated with less GI side effects. This will need to be further investigated in larger trials.

– Written by Shazli Azmi & Maryam Ferdousi

Reinert-Hartwall L, Honkanen J, Salo HM *et al*. Th1/Th17 Plasticity Is a marker of advanced β-cell autoimmunity and impaired glucose tolerance in humans. *J. Immunol*. 194(1), 68–75 (2015).

This study assessed the Th17 immunity and the degree of plasticity of Th17 cells in β-cell autoantibody-negative children, early islet autoimmunity (antibody-positive and normal blood glucose), advanced islet autoimmunity (long-term antibody-positive and impaired glucose tolerance) and diagnosed diabetic individuals by analyzing anti-CD3- and anti-CD28-stimulated PBMCs. Upregulation of IFN-γ, IL-9 and IL-17, and plasticity of Th17 cells were only seen in children with advanced β-cell autoimmunity and impaired glucose tolerance or clinical Type 1 diabetes. The IFN-γ/IL-17 mRNA ratio in Th17 cells correlated with HbA1c and plasma glucose concentrations in an oral glucose tolerance test performed in the children with advanced β-cell autoimmunity. These data suggest that Th17 cells contribute the damage of β-cell in combing with Th1 cells and the development of Th1/Th17 plasticity may serve as a biomarker of disease progression from b cell autoantibody positivity to overt Type 1 diabetes.

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