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Abbreviations used in this issue

BMI = body mass index
CV = cardiovascular
HbA1c = glycosylated haemoglobin
HR = hazard ratio
MI = myocardial infarction
RCT = randomised controlled trial
RYGB = Roux-en-Y gastric bypass
TSH = thyroid-stimulating hormone

Welcome to issue 112 of Diabetes and Obesity Research Review.

This issue begins with interesting research undertaken in monozygotic twins with differing BMIs assessing CV diseases and death. The healthcare costs for the Waitemata DHB for obese patients with diabetes before they undergo bariatric surgery, the costs of surgery itself and postoperative costs have been reported. Another cost analysis (this time from the US) has looked at the economic impact of maintaining versus gaining bodyweight in patients with type 2 diabetes. This issue concludes with a paper reporting an unexpectedly low rate of depression and major depressive disorder among adults with type 1 diabetes, and a high rate of false-positive results associated with use of the PHQ8 (eight-item Patient Health Questionnaire).

With just one more issue remaining for 2016, now is a great time to get your feedback and suggestions to us.

Best regards,

Associate Professor Jeremy Krebs
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Risks of myocardial infarction, death, and diabetes in identical twin pairs with different body mass indexes

Authors: Nordström P et al.

Summary: MI, type 2 diabetes and death risks were compared over a mean of 12.4 years of follow-up in a cohort of 4046 monozygotic twin pairs (median baseline age 57.6 years) with discordant BMI. Compared with leaner twins (mean BMI 23.9 kg/m²), the heavier twins (25.9 kg/m²) had lower risks of MI and death (5.0% vs. 5.2% and 13.6% vs. 15.6%, respectively; combined adjusted odds ratio 0.75 [95% CI 0.63, 0.91]), and the risk did not differ between twin pairs in which the heavier twin had a BMI of ≥30.0 kg/m² (65 pairs; 0.42 [0.15, 1.18]); however, the heavier twins were at increased risk of incident diabetes compared with their lighter counterparts (2.14 [1.61, 2.84]). Increases in BMI since 30 years before baseline did not increase later risk of MI or death (odds ratio 0.97 [95% CI 0.89, 1.05]) but did increase incident diabetes risk (1.13 [1.01, 1.26]).

Comment: What an interesting study. The question being whether obesity per se confers increased risk for CV disease and diabetes when the complexities of genetics are accounted for by studying monozygotic, identical twins who differ only by weight. Of course this doesn’t completely exclude any epigenetic factors that might come into play with increasing weight or environmental factors. The duration of follow-up is over 10 years, which should be long enough to see any important difference. The conclusion was that there was no increased risk of CV events, but there was a greater incidence of diabetes in the heavier twins. The main problem with this study is that the difference between BMI wasn’t that much and the mean BMI was only just above 25 kg/m². Having said that, in a subset of twins who were more discordant and heavier, the observations were the same. So these are interesting findings suggesting obesity may be more important for diabetes than CV disease.


Abstract

Independent commentary by Associate Professor Jeremy Krebs.

Associate Professor Krebs is an Endocrinologist with a particular interest in obesity and diabetes. He trained in Endocrinology at Wellington Hospital in New Zealand and then did his doctorate with the Medical Research Council - Human Nutrition Research unit in Cambridge England. His thesis was on the impact of dietary factors on obesity and insulin resistance. Assoc Prof Krebs returned to New Zealand in 2002 to take up a consultant Endocrinology post at Wellington Hospital, where he is Clinical Leader of Endocrinology and Diabetes. He is an Associate Professor with the University of Otago, and former Director of the Clinical Research Diploma at Victoria University - which he established. As well as clinical and teaching activities, Assoc Prof Krebs maintains active research interests in the area of obesity and diabetes, with a focus on nutritional aspects, bariatric surgery and diabetes service delivery.
Effects of testosterone treatment on body fat and lean mass in obese men on a hypocaloric diet

Authors: Ful MNT et al.

Summary: Men with BMI ≥30 kg/m² and a total testosterone level ≤12 nmol/L consumed a very low energy diet for 10 weeks followed by 46 weeks of weight maintenance, during which they received randomly assigned intramuscular testosterone undecanoate (n=49) every 10 weeks or placebo (n=51); there were 82 study completers. Compared with controls, testosterone recipients experienced greater reductions in fat mass (mean adjusted difference −2.9kg [p=0.04]) and visceral fat (−2678 mm² [p=0.04]). Although lean mass loss following the initial 10-week diet did not differ significantly between the testosterone and placebo groups (−3.9 vs. −4.8kg [p=0.36]), testosterone recipients significantly regained lean mass during the bodyweight maintenance phase (3.9kg [p<0.001]), whereas placebo recipients did not (0.8kg [p=0.29]), resulting in attenuated reduction in lean mass with testosterone versus placebo (mean adjusted difference 3.4kg ([p=0.002]).

Comment: In obesity, because of changes in sex hormone binding globulin, levels of total testosterone are often slightly reduced in men. It is controversial as to whether this has any important clinical effect, and for most men weight loss rather than testosterone supplementation is the recommended management. This study is therefore interesting. Here men undergoing weight loss with a very low energy diet who had testosterone levels below the reference range were randomised to receive testosterone or placebo, with the primary outcome being change in body composition after 12 months. Testosterone promoted greater loss of fat mass and in the weight maintenance phase regained and preserved lean mass. This certainly warrants further research, although we must be very cautious before recommending such an approach in clinical practice.

Abstract

Thyroid function and risk of type 2 diabetes

Authors: Chaker L et al.

Summary: Relationships between thyroid function and diabetes were explored in this population-based prospective cohort of 8452 participants. There were 798 cases of diabetes in the cohort over mean 7.9 years of follow-up. Each log increase in TSH (thyroid-stimulating hormone) level was associated with a significant increase in diabetes risk (HR 1.13 [95% CI 1.08, 1.18]), even within the reference range of thyroid function (1.24 [1.06, 1.45]), and each 1 pmol/L increase in free T4 (thyroxine) level was associated with a lower diabetes risk (0.96 [0.93, 0.99]), including those within the reference range of thyroid function (0.96 [0.92, 0.99]). Similarly, progression from prediabetes to diabetes was increased with low-to-normal thyroid function (HRs 1.32 [95% CI 1.06, 1.64] and 0.91 [0.86, 0.97] for TSH and free T4, respectively). The absolute risk of progressing from prediabetes to type 2 diabetes fell from 35% to around 15% with higher free T4 levels within the normal range.

Comment: All of my endocrinology biases are being challenged this month! Subclinical or borderline hypothyroidism is so often mooted as the cause of many an ailment, but there is a distinct lack of convincing evidence to support these claims. This observational cohort study examined the relationship between thyroid function and incident type 2 diabetes, and found an association between higher TSH and risk of diabetes, and conversely lower free T4 and diabetes – a relationship that persists even within the reference range for TSH and T4. With its metabolic function and association with acute weight change, thyroid hormone could well play a role, or could simply be a marker of other drivers. Once again, beyond the setting of research and call for a prospective RCT, this study is of interest but does not support a call for use of thyroid hormone supplementation in those with prediabetes.

Abstract

Winner of the NZMA Anatomy Prize Draw is Piotr Gawor. The prize is a $300 Prezzy Card.
Effectiveness of the influenza vaccine in preventing admission to hospital and death in people with type 2 diabetes

Authors: Vamos EP et al.

Summary: The effectiveness of influenza vaccination for preventing hospitalisations for acute CV and respiratory conditions and death from any cause in patients with type 2 diabetes was evaluated using primary and secondary care data from a retrospective cohort of 124,503 adults with type 2 diabetes in England. Compared with vaccine nonrecipients, vaccine recipients were older and had more comorbidities. Over 623,591 person-years of observation, vaccination was associated with significantly lower rates of hospitalisation for stroke (adjusted incidence rate ratio 0.70 [95% CI 0.53, 0.91]), heart failure (0.78 [0.65, 0.92]) and pneumonia or influenza (0.85 [0.74, 0.99]), significantly lower all-cause mortality (0.76 [0.65, 0.83]) and a nonsignificant reduction in acute MI (0.81 [0.62, 1.04]) during influenza seasons.

Comment: Many guidelines call for routine influenza vaccination for people with diabetes. This study supports those recommendations. Although this is a retrospective cohort study with the obvious potential biases and confounders, the relative risk for those receiving the influenza vaccination compared with those who didn’t for all outcomes was impressive. Recipients had a 20–30% lower rate of admission to hospital for stroke, heart failure, pneumonia and all-cause death. With vaccination now so widely available, we should be promoting this as a regular winter tonic for all those with type 2 diabetes!

Reference: CMAJ 2016;188(14):E342–51

Costs of bariatric surgery in a randomised control trial (RCT) comparing Roux en Y gastric bypass vs sleeve gastrectomy in morbidly obese diabetic patients

Authors: Gounder ST et al.

Summary: The direct healthcare costs (hospital clinic visits, perioperative care, hospitalisations and medications) in NZ for laparoscopic sleeve gastrectomy and laparoscopic RYGB (Roux-en-Y gastric bypass) surgery were examined in the context of an RCT enrolling Waitemata DHB patients with type 2 diabetes; 58 participants underwent laparoscopic sleeve gastrectomy and 56 underwent laparoscopic RYGB. The mean cost per patient 1 year before enrolment was $1789, the mean per-patient surgical costs were $29313 and $12,456 for laparoscopic sleeve gastrectomy and laparoscopic RYGB, respectively, and the mean cost per patient 1 year postoperatively was $4760. There was a significant reduction in mean medication cost per patient during the 2012–2014 prevalence.

Comment: With a third of New Zealanders being obese and at risk of major associated morbidity, the costs to the health system let alone the individual must be considered when planning services and interventions. Bariatric surgery is an important option for many with obesity, particularly when complicated by diabetes. There is growing evidence for health benefit, but relatively little evidence around the economics of this, particularly in the NZ context. This study is therefore very helpful in providing an analysis of the health system costs of two commonly performed bariatric procedures. Not surprisingly the costs in the first year after surgery are higher than in the year preceding. However, the major reduction in medication costs is likely to be cumulative and ongoing, such that a comparison at 10 years postsurgery would be of great interest.


Medical care costs associated with long-term weight maintenance versus weight gain among patients with type 2 diabetes

Authors: Nichols GA et al.

Summary: These authors calculated the economic impact of maintaining bodyweight versus gaining weight over 4 years in 8154 patients with type 2 diabetes, with the following four groups analysed: weight change <5% and HbA1c level <7%; weight gain ≥5% and HbA1c level <7%; weight change <5% and HbA1c level ≥7%; and weight gain ≥5% and HbA1c level ≥7%. They found that costs fell by about $US400 regardless of HbA1c level in patients who maintained their weight within 5% of baseline, whereas costs increased significantly by $1473 in patients who gained ≥5% of baseline weight and had a mean HbA1c level ≥7%, and increased modestly but nonsignificantly by $387 in those who gained ≥5% with mean HbA1c level of <7%.

Comment: This paper somewhat relates to the previous one on bariatric surgery, but looked at costs related to weight change and glycaemic control in people with type 2 diabetes. In this large cohort, maintenance of weight over time was related to a reduction in costs versus those who gained weight, particularly if they also had poor glycaemic control. Whilst this is through diet and lifestyle advice rather than bariatric surgery, it certainly aligns with the NZ evidence of reduced medication costs with significant weight loss. Perhaps as the authors suggest, a primary goal could be avoidance of weight gain, which is likely more achievable than weight loss.


BMI at age 17 years and diabetes mortality in midlife

Authors: Twigg G et al.

Summary: The relationship between BMI during late adolescence and diabetes-associated mortality in midlife was explored using data from 2,294,139 Israelis. There were 481 diabetes-related deaths during 42,297,007 person-years of follow-up, and the mean age at death was 50.6 years. A graded increase in diabetes mortality was seen from the 5–24th BMI percentiles, participants from the 50–74th, 85–94th (overweight) and ≥95th (obese) percentiles were at significantly increased risk of death attributable to diabetes (respectively adjusted HRs 1.6 [95% CI 1.1, 2.3], 8.0 [5.7, 11.3] and 17.2 [11.9, 24.8]; sensitivity analyses did not affect the findings). The estimated population-attributable fraction for diabetes mortality increased from 31.2% for the 1967–1977 prevalence of overweight and obesity at age 17 years to 52.1% for the 2012–2014 prevalence.

Comment: Many previous studies have shown an association between obesity in childhood and adolescence and subsequent adverse health outcomes in adulthood. This study adds to that evidence. It draws on large population data from Israel, with BMI measured in late adolescence and subsequent death related to diabetes over a median follow-up period of 18 years. There was a graded increase in risk for overweight and obese individuals compared with those of normal weight, with mean age of death just 50 years. These data again support calls for action on childhood obesity as a priority for preventing subsequent poor outcomes. It is pleasing to see increased recognition of this need by the government and a move in the right direction to address this. More is required.

**Changes in overall diet quality and subsequent type 2 diabetes risk**

**Authors:** Ley SH et al.

**Summary:** Using data from the US Nurses’ Health Study I and II and the Health Professionals Follow-up Study, these researchers sought to evaluate diet quality changes during a 4-year period and subsequent type 2 diabetes incidence over 4 years. Among the 124,607 participants free of diabetes at baseline who were followed for ≥20 years (2,093,416 person-years), 9361 cases of type 2 diabetes occurred. The risk of developing diabetes was greater in participants with a >10% decrease in AHEI (Alternate Healthy Eating Index) score over 4 years (adjusted HR 1.34 [95% CI 1.23, 1.46]), whereas the risk was decreased in those with a >10% increase in AHEI score (0.84 [0.78, 0.90]). Greater improvements in diet quality were associated with lower diabetes risk across baseline diet quality status and BMI (p<0.01 for trend for both). Bodyweight change explained 32% of the association between AHEI score change and diabetes risk.

**Comment:** These large US prospective cohort studies continue to give us a wealth of population data. This is an analysis of the relationship between change in dietary pattern over time and incident type 2 diabetes. Using a global score of healthy eating, improvement in dietary quality was associated with a significant reduction in incident diabetes whilst deterioration of diet was associated with increased risk. Notably this was independent of the starting point of the diet, and was across all weight groups. However, one-third of the increased risk with worsening diet was explained by weight gain, meaning that the majority of the excess risk was due to the dietary pattern itself. This in turn suggests that improving dietary quality independent of weight change is likely to confer a reduced risk of developing diabetes.


**Lactic acidosis: relationship between metformin levels, lactate concentration and mortality**

**Authors:** Boucaud-Maitre D et al.

**Summary:** These authors reported on 727 cases of lactic acidosis in metformin recipients spontaneously reported in a pharmacovigilance database; metformin plasma concentrations were documented for 260 patients, lactate plasma levels for 556, pH for 502, creatinine level for 397 and the vital outcome for 713. Metformin plasma concentration, lactate level, pH and plasma creatinine level were all significantly correlated. Compared with deceased patients, survivors had significantly lower metformin plasma concentrations (25.2 vs. 37.4 mg/L [p=0.002]) and lactate levels (10.8 vs. 16.3 mmol/L [p<0.001]), and a significantly greater proportion of patients with a metformin concentration >5 vs. <5 mg/L died (30% vs. 11% [p=0.003]).

**Comment:** OK I will take a balanced approach to metformin. For those who regularly read this review, you will know my frustration with what I regard as an unnecessary paranoia about metformin and lactic acidosis. However, this paper is important to acknowledge. From French pharmacovigilance data in over 700 cases of lactic acidosis in people on metformin therapy, there is evidence that a higher plasma metformin concentration was associated with a higher lactate level, and with greater risk of death. This was also related to higher creatinine level and therefore greater risk of metformin accumulation. Taken together I see this as a warning that in those with renal impairment, be it acute or chronic, in a clinical setting where an individual is at risk of developing lactic acidosis, such as sepsis or hypoxia, extreme caution should be exercised with metformin. These are the situations we should be wary of, not the common day-to-day use of metformin.


**Prevalence of depression in type 1 diabetes and the problem of over-diagnosis**

**Authors:** Fisher L et al.

**Summary:** Depression and diabetes distress was assessed in 863 adults with type 1 diabetes in this research. The participants completed the PHQ8 depression scale, the type 1 Diabetes Distress Scale and the SCID (Structured Clinical Interview for DSM Disorders) to assess major depressive disorder. The respective prevalence rates of depression according to PHQ8 scores ≥10, ≥12 and ≥15 and a positive DSM (Diagnostic and Statistical Manual of Mental Disorders) algorithm result were 11.4%, 7.1%, 3.8% and 4.6%. The major depressive disorder prevalence was 3.5%, and the prevalence of at least moderate diabetes distress was 42.1%. False-positive rates using PHQ8 versus SCID were 52–71% depending on the criterion used. Among patients depressed according to PHQ8 or SCID, 92.3–96.2% also reported increased diabetes distress. There was no significant association seen between any group with depression according to PHQ8 or SCID and HbA1c level, but depression was associated with more other life stress, more complications and a lower level of education.

**Comment:** It is commonly stated that depression is more common in both those with type 1 and type 2 diabetes. Type 1 diabetes, frequently diagnosed at a young age, has major daily demands on the person, both emotionally and physically. The recently coined term ‘diabetes distress’ is very descriptive of the not unexpected response of many of those with type 1 diabetes to these unrelenting demands. What this paper is suggesting is that depending on how you assess for depression, there may have been an overestimation in rates, when those with diabetes distress, without some of the more debilitating aspects of true depression, get misclassified. That is not to underestimate the psychological effects of diabetes, but rather to recognise some subtleties of the nature and severity of them.