Diabetes & Obesity Research Review™

Making Education Easy

Issue 84 – 2014

In this issue:

Welcome to issue 84 of Diabetes and Obesity Research Review.

Among more traditional research papers on diabetes and its management, this issue includes a number of reviews and commentary papers, at least one of which I'm sure will ignite considerable debate – a BMJ article on the prediabetes epidemic. I have also included a fascinating discussion on the role of the gut microbiome in obesity and its related comorbidities, including the role of chronic inflammation. This issue concludes with a review of studies looking at workstation alternatives that are designed to increase energy expenditure.

I hope this issue provides interesting reading for you and, as always, I invite you to send your comments, feedback and suggestions.

Best regards,

Dr Jeremy Krebs
jeremykrebs@researchreview.co.nz

Glycemic goals in diabetes: trade-off between glycemic control and iatrogenic hypoglycemia

Author: Cryer PE

Summary: This paper discussed the compromise between the documented up- and downsides of glycaemic control with respect to the selection of a glycaemic goal in an individual with diabetes. The author noted that hypoglycaemia is only an issue when glycaemic control is achieved with agents with the potential to cause hypoglycaemia (i.e. a sulfonylurea, a glinide, insulin) or without substantial bodyweight loss, particularly in the setting of absolute endogenous insulin deficiency. In such cases, the glycaemic goal should be linked to the hypoglycaemia risk. A reasonable individualised glycaemic goal was proposed of lowest Hb_{A1c} level that does not result in severe hypoglycaemia and preserves awareness of hypoglycaemia, with minimal or no symptomatic or even asymptomatic hypoglycaemia.

Comment: The trade-off of glycaemic control versus hypoglycaemia in the management of type 2 diabetes has been a highly discussed issue, particularly since the publication of the ACCORD study. It has galvanised the call to individualise targets and therapies, and this is now the central theme of international guidelines. It also fuels the debate over which glucose-lowering therapies are the most appropriate, particularly as newer agents such as PPAR (peroxisome proliferator-activated receptor)-γ agonists, DPP (dipeptidyl peptidase)-4 antagonists, GLP (glucagon-like peptide)-1 analogues and SGLT (sodium glucose cotransporter)-2 antagonists do not stimulate insulin release, and therefore are not directly responsible for causing hypoglycaemia. This commentary paper is a very good summary and discussion of these issues.

Reference: Diabetes 2014;63(7):2188–95

Abstract

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Overfeeding polyunsaturated and saturated fat causes distinct effects on liver and visceral fat accumulation in humans

Authors: Rosqvist F et al.

Summary: The LIPOGAIN trial randomised 39 young individuals of normal bodyweight to overeat muffins high in palm oil (a saturated fatty acid source) or sunflower oil (an n-6 polyunsaturated fatty acid source) for 7 weeks. While bodyweight gain in both groups was similar, compared with polyunsaturated fatty acid consumption, saturated fatty acid consumption was associated with a marked increase in liver fat, a 2-fold larger increase in visceral adipose tissue, and an approximately one-third smaller increase in lean tissue. Liver fat increases were directly correlated with plasma saturated fatty acid levels and inversely with polyunsaturated fatty acid levels. Genes that regulate energy dissipation, insulin resistance, body composition and fat-cell differentiation in abdominal subcutaneous adipose tissue were found to be differentially regulated between the two diets, and were associated with increased polyunsaturated fatty acid levels in abdominal subcutaneous adipose tissue.

Comment: The differential effects of saturated fat and polyunsaturated fat on metabolic and cardiovascular health have been well described in epidemiological and some experimental studies. The strong association between saturated fat intake and risk for diabetes has underpinned dietary recommendations to limit saturated fat to <10% of total energy intake. This study takes a more detailed look at the effects of excess energy intake as either saturated or polyunsaturated fat. The findings are quite remarkable with very clear differences in how the body partitions the different fatty acids. Excess saturated fat increases hepatic and visceral fat, which are known to have adverse metabolic consequences. This provides supportive evidence to recommendations to substitute polyunsaturated fats for saturated fat.

Reference: Diabetes 2014;63(7):2356–68
Abstract

Risk of type 1 diabetes progression in islet autoantibody-positive children can be further stratified using expression patterns of multiple genes implicated in peripheral blood lymphocyte activation and function

Authors: Jin Y et al.

Summary: The potential of gene expression profiles as biomarkers for risk stratification was explored in 104 autoantibody-positive DAISY (Diabetes Autoimmunity Study in the Young) participants using discovery and validation datasets based on microarray and real-time PCR (polymerase chain reaction), respectively. The microarray data included 454 candidate genes with expression levels associated with various type 1 diabetes progression rates, and real-time PCR of the top 27 candidate genes showed five (**B**ACH2, **I**GLL3, **C**DC20, **T**XNDC5, **E**IF3A) that were associated with differential progression and implicated in lymphocyte activation and function. Multivariate analyses of these five genes in both datasets revealed four multigene models (BI, ICE, BICE, BITE) that could consistently stratify high- and low-risk subsets of autoantibody-positive subjects (hazard ratios >6 [p<0.01]).

Comment: We are increasingly seeing the progress made in genomics coming to fruition in more clinical applications. Whilst this study is some way off from this, it does demonstrate how applied genomics may enhance clinical risk stratification and decision making. Better risk prediction will enable more informed counselling not only for those who are at greatest risk, but also those who may be more reassured. It will also enable the best targeting of potential interventions to prevent progression to type 1 diabetes. Furthermore it may be hypothesis generating to better understand the pathogenic pathway for type 1 diabetes. This may also open up potential targets for drug development.

Reference: Diabetes 2014;63(7):2506–15
Abstract

The effects of a Mediterranean diet on the need for diabetes drugs and remission of newly diagnosed type 2 diabetes

Authors: Esposito K et al.

Summary: This paper reported >4-year follow-up of a trial that had randomised overweight, middle-aged patients with newly diagnosed type 2 diabetes to consume a low-carbohydrate Mediterranean diet (n=108) or a low-fat diet (n=107). The primary endpoint (need of antidiabetic medication) had been reached in all Mediterranean diet and low-fat diet group participants after total follow-up periods of 8.1 and 6.1 years, respectively, and the respective median survival times were 4.8 and 2.8 years. Compared with the low-fat group, participants in the Mediterranean diet group were more likely to experience partial or complete diabetes remission at years 1 and 6 (14.7% vs. 4.1% and 5.0% vs. 0%, respectively).

Comment: There have been a number of studies published over the last couple of years reporting the benefits of a Mediterranean diet on weight loss and glucose metabolism. This has focussed attention on the concept of dietary patterns rather than specific macronutrients, which have been the focus for the last 15–20 years. This report extends a previously reported study comparing a low-carbohydrate Mediterranean diet with a low-fat diet in those with newly diagnosed type 2 diabetes. In this analysis the Mediterranean diet was superior for glycaemic outcomes over 6 years. This strongly supports including this dietary approach as one option for patients to adopt. Choosing a dietary pattern and therefore particular foods may be easier to follow and adhere to than trying to transform macronutrient percentages into food choices.

Reference: Diabetes Care 2014;37(7):1824–30
Abstract

Musculoskeletal complications in type 1 diabetes

Authors: Larkin ME et al., the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group

Summary: This cross-sectional analysis identified the presence of cheiroarthropathy (adhesive capsulitis, carpal tunnel syndrome, flexor tenosynovitis, Dupuytren's contracture or a positive prayer sign) in 66% of 1217 participants from the DCCT/EDIC (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications) cohort followed for an average of 24 years. No significant difference was seen between the trial's intensive and conventional therapy arms for the prevalence of cheiroarthropathy (64% and 68%, respectively [p=0.1640]), but cheiroarthropathy was significantly associated with age, sex, diabetes duration, skin intrinsic fluorescence, Hb_{A1c} level, neuropathy and retinopathy ($p<0.005$ for all). Participants with cheiroarthropathy had significantly worse DASH (Disabilities of the Arm, Shoulder and Hand) functional disability scores than those without cheiroarthropathy ($p<0.0001$).

Comment: When we think about diabetes-related complications, we commonly think about retinopathy, nephropathy and neuropathy, but often forget some of the less prominent complications. Progressive thickening of soft tissues such as can occur in the hands, including carpal tunnel syndrome, capsulitis, tenosynovitis, Dupuytren's contracture and positive prayer sign, are examples. This study reported the prevalence of these complications in the DCCT cohort. The prevalence was a remarkable 66% after >20 years of diabetes. This was related not only to duration, but also to glycaemic control. It would be interesting to know whether similarly high rates are seen in patients with type 2 diabetes. Soft tissue complications are clearly very common and we should remember to check for them, particularly when our patients have had diabetes for a long time.

Reference: Diabetes Care 2014;37(7):1863–9
Abstract

Effect of early multifactorial therapy compared with routine care on microvascular outcomes at 5 years in people with screen-detected diabetes

Authors: Sandbæk A et al.

Summary: In the ADDITION-Europe trial, 3057 patients with screen-detected diabetes from 343 general practices were randomised by cluster to early multifactorial intensive therapy or routine care. This analysis of 2861 eligible participants reported microvascular complications 5 years after diagnosis. No significant difference was seen between the intensive treatment versus routine care groups at 5 years for albuminuria of any kind (22.7% vs. 24.4%; odds ratio 0.87 [95% CI 0.72, 1.07]), retinopathy (10.2% vs. 12.1%; 0.84 [0.64, 1.10]) or neuropathy (4.9% vs. 5.9% [0.68, 1.34]). Increases in baseline estimated glomerular filtration rate were seen at follow-up in the intensive treatment and routine care groups (4.31 and 6.44 mL/min, respectively).

Comment: Well this is a bit disappointing! Diabetes teams have taken the findings of UKPDS, which showed that intensive glycaemic control in those with newly diagnosed type 2 diabetes reduces microvascular complications, and used them to inform the design and implementation of screening and treatment systems. Furthermore, the Steno 2 trial showed that a multifactorial intervention in those at high risk of complications was particularly beneficial in reducing these. In this study, primary care practices were randomised to either structured intensive management or routine care. Surprisingly, there were no differences in multiple diabetes complication outcomes over 5 years. One explanation for this may be that routine care has been brought up to the level of the more intensive management on the background of the well-publicised findings of these major trials. Alternatively, despite organisational systems, the necessary changes in behaviour of both patients and healthcare teams may not have been achieved. Perhaps it's time to rethink the approach.

Reference: Diabetes Care 2014;37(7):2015–23
Abstract

Diabetes & Obesity Research Review

Independent commentary by Dr Jeremy Krebs, Endocrinologist & Clinical Leader at Wellington Hospital. He is also a Senior Clinical Lecturer with the University of Otago, and Director of the Clinical Research Diploma at Victoria University.

For full bio CLICK HERE.

The epidemic of pre-diabetes: the medicine and the politics

Authors: Yudkin JS & Montori VM

Summary: This BMJ article discussed a number of important points regarding prediabetes. The authors started by making the observation that strategies aimed at slowing the increasing prevalence of diabetes have focused on identifying at-risk groups. They discussed the changing definition of at-risk groups from solely patients with impaired glucose tolerance to include those with raised fasting glucose or Hb_{A1c} levels, and the lowering of cutoff levels, which has increased the prevalence of prediabetes 2- to 3-fold. They also noted that predicting progression to diabetes is better for impaired glucose tolerance than for fasting glucose and Hb_{A1c} levels. They also discussed the assumption that treating individuals in the newly defined categories will result in mortality and morbidity improvements, noting that no studies have examined the effect of lifestyle or drug interventions in patients in the newly added subcategories. They presented evidence of overdiagnosis (e.g. over half of all Chinese adults now have 'prediabetes') and its associated harms (e.g. problems with self-image, insurance, employment and healthcare burdens and costs).

Comment: I have included this article to promote debate. There are two sides to this issue and I don't believe there is a clear answer. Is prediabetes a real and important entity, or are we defining a disease that doesn't exist? The difficulty arises in part because we are taking a continuous biological variable and trying to ascribe a threshold above which there is a clear, predictable and reproducible risk for adverse outcomes. Yudkin advances the argument that the older definition of impaired glucose tolerance defined in 1979 from the oral glucose tolerance test has better predictive power than newer Hb_{A1c}-based definitions. This ignores the poor characteristics of the oral glucose tolerance test as a reproducible test, or the difficulty getting people to do it properly. Nonetheless, this is a thought-provoking paper that challenges us to think about the real meaning and place of prediabetes.

Reference: BMJ 2014;349:g4485
Abstract

Are bedtime nutritional strategies effective in preventing nocturnal hypoglycaemia in patients with type 1 diabetes?

Authors: Desjardins K et al.

Summary: These authors analysed data from 16 studies on nutritional strategies to prevent nocturnal hypoglycaemia in patients with type 1 diabetes. While the overall evidence level was low, the current data show that a calibrated bedtime snack based on bedtime blood glucose level could reduce nocturnal hypoglycaemic episodes in patients treated with human or animal insulin, but evidence for patients treated with insulin analogues as part of multiple daily injections or an insulin pump regimen is lacking. There is also some evidence suggesting that bedtime snacks including uncooked corn-starch or alanine could help prevent nocturnal hypoglycaemia. The authors suggest individualised recommendations of bedtime snacking for patients or situations where the risk for nocturnal hypoglycaemia is high.

Comment: Nocturnal hypoglycaemia can be a major problem for people with both type 1 and type 2 diabetes. Prior to the development of long-acting insulin analogues, nocturnal hypoglycaemia would often limit the ability of a person to achieve tight glycaemic control. A bedtime snack to allow adequate insulin doses to achieve good fasting glucose levels without hypoglycaemia was commonly recommended. This present review of the literature sought to find the evidence to support this. Perhaps not surprisingly, there is very little high quality evidence to support any particular snack strategy, and none for regimens with analogue insulins or for insulin pump therapy. This does not mean that a bedtime snack may not be appropriate for some individuals, but it is an evidence-free zone. A well-conducted study could be very valuable.

Reference: Diabetes Obes Metab 2014;16(7):577–87
Abstract

Gut microbiome, obesity-related comorbidities, and low-grade chronic inflammation

Author: Tarantino G

Summary: The author of this paper commented that elucidating the mechanisms involved in inducing and maintaining obesity are critical if we are to reduce risks associated with obesity, particularly given its high prevalence in many populations. He also noted that while reversing insulin resistance by weight loss is often achievable through lifestyle interventions and bariatric surgery, *"genetic assets can exceed these favorable changes"*. Moreover, the findings from a number of studies that have looked at the impact of the gut microbiome, including the role of chronic low-grade inflammation, cast doubt regarding the *"absolute necessity for weight loss in obese patients"* for reducing inflammation and obesity-related comorbidities.

Comment: Isn't it amazing that there are more microbial cells in the human body than human cells! So does that actually make us parasites on our microbes? The impact of the microbiome on health is becoming a very hot area of research, and none more so than in the area of obesity and diabetes. For those who have never considered this area before, this paper is a nice summary of how the microbiome may be a factor in the aetiology of obesity and diabetes and some of the data that support this hypothesis. Perhaps most interesting is the notion that changing the microbiome by either pre- or probiotics, or even more radically by so-called faecal transplants, has the potential to reverse the effects on weight and glucose metabolism. The mind boggles!

Reference: J Clin Endocrinol Metab 2014;99(7):2343–6
Abstract

Changing the way we work: elevating energy expenditure with workstation alternatives

Authors: Tudor-Locke C et al.

Summary: These authors evaluated 57 articles that focussed on use of energy-expending alternatives for workstations during simulated or real work tasks. Compared with traditional seated workstations, sitting on a stability ball or use of sit-stand/standing desks had little effect on energy expenditure (~1.2 kcal/min) or on work task performance, while treadmill and pedal desks increased energy expenditure by ~2–4 kcal/min, but with evidence of work task impairment, particularly tasks requiring finer motor skills. Although users are generally open to the idea of workstation alternatives, evidence of less than optimal use was seen. The authors concluded that active workstations *"represent a potential strategy for mitigating the diminished energy expenditure inherent to contemporary office-based workplaces, but only if they are scalable"*.

Comment: Sedentary behaviour as encouraged by seated desk-based jobs has been shown to be an important contributor to obesity and associated diabetes. The idea of workstations that can reduce the sedentary nature of such jobs is very appealing. This review discussed the issues around this, including the potential increases in energy expenditure, and also the potential negative impact on functionality. Incidental exercise has real potential to increase total energy expenditure over a day. I have been interested in the idea of conducting standing clinics in the outpatients to 'walk the talk' with our patients. I haven't quite managed to roll this out yet, but watch this space.

Reference: Int J Obes 2014;38(6):755–65
Abstract