Diabetes & Obesity Research Review™

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In this issue:

Welcome to issue 34 of Diabetes and Obesity Research Review.

This issue includes some new analyses of data from large, prominent trials. The ACCORD study is in the spotlight again, with an analysis of the impact of intensive blood glucose lowering on health-related quality of life (HRQOL). An analysis of >17,000 nondiabetic EPIC study participants challenges previously reported associations between low Hb_{A1c} levels and increased mortality risk. The risk of incident type 2 diabetes was shown to be increased by smoking (including passive) among women who had participated in the Nurses study.

We hope you find the papers selected for this issue stimulating reading, and we welcome your comments and feedback.

Kind Regards,

Prof Peter Little

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Recovery of β-cell functions with low-dose insulin therapy: study in newly diagnosed type 2 diabetes mellitus patients

Authors: Bhattacharya S et al

Summary: In this study, 20 patients with newly diagnosed type 2 diabetes mellitus without acute or chronic complications received premixed insulin (70/30) 16U started as two divided doses and continued until normoglycaemia was achieved, after which the dose was titrated down. Near-normoglycaemia was achieved at 3 months, while plasma insulin and C-peptide levels increased slowly and steadily until month 4, after which they remained stable during 2 months of follow-up. Glycosylated haemoglobin (Hb_{A1c}) decreased from 11.3% at diagnosis to 7.05% at 6 months. The participants' mean bodyweight decreased from 70kg to 68kg at 3 months, and at 6 months, their total cholesterol, LDL cholesterol and triglyceride levels had decreased and their HDL cholesterol level had increased.

Comment (NC/PL): The traditional Western approach to newly diagnosed (obese) type 2 diabetes is a period of lifestyle interventions being diet and exercise. In Asia, there is a propensity to try early insulin therapy. This small study from New Delhi and using a local population used premixed insulin in newly diagnosed type 2 diabetes until normoglycaemia was achieved and then the insulin dose was titrated down. The regimen produced β-cell recovery, which was maintained at 6 months. A current Australian view would doubt the voracity of this 'early insulin' approach on three grounds: firstly, the trials compared intensive treatment with less intensive treatment and the likely benefits are due to changes in glucose toxicity and nothing to do with the agent being used; secondly, the UKPDS answers this question with direct comparison between Hb_{A1c} outcomes using metformin, insulin and sulphonylureas from diagnosis where there was no difference; and thirdly, insulin is less well accepted, has a higher incidence of hypoglycaemia and has associated costs. There is insufficient justification for serious adoption of this strategy in Australia at this time.

Reference: Diabetes Technol Ther 2011;13(4):461–5
http://www.liebertonline.com/doi/abs/10.1089/dia.2010.0187

Effect of intensive glycemic lowering on health-related quality of life in type 2 diabetes: ACCORD trial

Authors: Anderson RT et al, for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Investigators

Summary: ACCORD trial data were analysed to compare HRQOL outcomes between 1956 participants who received intensive or standard glycaemic control strategies for type 2 diabetes mellitus and completed the 36-item Short Form Health Survey (SF-36), the Diabetes Symptom Distress Checklist, the Patient Health Questionnaire-9 (PHQ-9) and the Diabetes Treatment Satisfaction Questionnaire (DTSQ) at baseline. Compared with standard glycaemic control, intensive glycaemic control was associated with a significantly larger decrease in SF-36 physical health component scores (–1.6 vs. –1.1; p=0.0345) and significant improvements in treatment satisfaction (DTSQ scores; p=0.0004). No between-group differences were seen for Diabetes Symptom Checklist or PHQ-9 scores, and there were no significant HRQOL effects of participant transition after discontinuation of intensive glycaemic control.

Comment (NC): The effect of intensifying treatment in type 2 diabetes on QOL measures is not clear, and there is a concern amongst clinicians that complex therapies are associated with reduced QOL. The ACCORD trial was a good test of this, as intensive treatment targeted Hb_{A1c} <6.0%. The results of the HRQOL substudy did not show a reduction in QOL measures in the intensive group compared with conventional treatment, and there was a small increase in diabetes treatment satisfaction. It must be remembered that this was a clinical trial with a selected group of patients, but perhaps what this teaches us is that complex treatment regimens are feared more by clinicians than the patients.

Reference: Diabetes Care 2011;34(4):807–12
http://care.diabetesjournals.org/content/34/4/807.abstract

Intradermal microneedle delivery of insulin lispro achieves faster insulin absorption and insulin action than subcutaneous injection

Authors: Pettis RJ et al

Summary: Ten healthy male volunteers received intradermal injections of insulin lispro 10IU daily on days 1 to 4 using microneedle lengths of 1.25, 1.5, 1.75 and 1.5mm, respectively, and SC administration on day 5 under euglycaemic clamp conditions to compare the pharmacokinetics and pharmacodynamics of the two routes of administration. Compared with SC injections, the intradermal microneedle injections were associated with: i) a shorter time to maximum concentration (C_{max}; 36.0–46.4 vs. 64.3 min; p<0.05); ii) greater fractional availability at early postinjection times; and iii) significantly shorter times to maximal, early half-maximal and late-half maximal (faster onset of insulin action) glucose infusion rates (GIR; 106–112 vs. 130 min [p<0.05], 29–35 vs. 42 min and 271–287 vs. 309 min, respectively) and increased GIR area under the curve. Relative total insulin bioavailability did not differ between injection routes. Different needle lengths did result in some variation in the pharmacokinetic and pharmacodynamic parameters. Although some transient, localised formation of wheals and redness were seen at intradermal injection sites, intradermal injections were generally well tolerated.

Comment (NC): One of the barriers to tight glycaemic control in type 1 diabetes is the relatively slow onset and offset of rapid-acting insulin when administered subcutaneously. This study trialled intradermal insulin injections in nondiabetics and resulted in a more rapid absorption of insulin compared with SC injections. This is promising, and may translate into improved postprandial glucose control and reduced hypoglycaemia. Further studies will hopefully look at this delivery system in patients with diabetes to assess how practical these injections are, the degree to which they may benefit glycaemic control and whether absorption is affected by larger insulin doses.

Reference: Diabetes Technol Ther 2011;13(4):435–42
http://www.liebertonline.com/doi/abs/10.1089/dia.2010.0184

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Independent commentary by Professor Peter Little and Dr Neale Cohen.

Peter Little is Professor and Head of Pharmacy and Leader, Diabetes Complications Group, Health Innovations Research Institute at RMIT University, Bundoora, Victoria. Peter is a past national President of Diabetes Australia.

Dr Cohen is a physician specialising in Diabetes and Endocrinology, and is currently the General Manager of Diabetes Services at the Baker IDI Heart and Diabetes Institute.

Beta cell function following 1 year vildagliptin or placebo treatment and after 12 week washout in drug-naive patients with type 2 diabetes and mild hyperglycaemia

Authors: Foley JE et al

Summary: Drug-naïve patients with type 2 diabetes mellitus and mild hyperglycaemia (aged ≥30 years, Hb_{A1c} ≤7.5%, BMI 22–45 kg/m²) were randomised to receive vildagliptin 100mg (n=29) or placebo (n=30) for 52 weeks, followed by a 12-week washout period, in this study. The primary efficacy variable of combined hyperglycaemia and arginine-stimulated C-peptide secretion (an assessment of β-cell function) increased by 5.0 nmol/L×min in the vildagliptin arm, compared with a decrease of 0.8 nmol/L×min in the placebo arm (p=0.03), but no significant between-group difference was seen after the washout period. Neither change in baseline Hb_{A1c} nor fasting glucose level differed significantly between the two arms at 52 weeks.

Comment (NC): Dipeptidylpeptidase-4 inhibitors are known to improve glycaemic control by increasing incretin levels. There is some evidence from animal studies that they may increase β-cell mass and function. If this proves to be the case in humans, it will have implications beyond blood glucose lowering, and these drugs may alter the natural history of type 2 diabetes. This study is disappointing in that there was no improvement in β-cell function compared with placebo after 12 months on vildagliptin. However, this is not the end of the story as longer term trials are needed. Furthermore, stimulated C-peptide secretion is a surrogate for β-cell function, and long-term Hb_{A1c} stability will be the ultimate test.

Reference: Diabetologia 2011 (Online First)
http://www.springerlink.com/content/jx4040050h141070/fulltext.html

No evidence of an increased mortality risk associated with low levels of glycated haemoglobin in a non-diabetic UK population

Authors: Pfister R et al

Summary: These researchers analysed the shape of the relationship between Hb_{A1c} and mortality risk in 17,196 participants from the European Prospective Investigation into Cancer and Nutrition (EPIC) study without known cardiovascular disease or diabetes. 1953 participants died during a median follow-up of 11.2 years. Compared with a reference Hb_{A1c} range of 5.0–<5.5%, ranges of <4.5%, 4.5–<5.0%, 5.5–<6.0%, 6.0–<6.5% and ≥6.5% were associated with all-cause mortality hazard ratios of 0.94 (95% CI 0.72–1.22), 0.99 (0.86–1.13), 1.10 (1.02–1.19), 1.29 (1.14–1.46) and 1.45 (1.16–1.80), respectively; spline regression showed an almost constant hazard ratio for all-cause mortality in the low Hb_{A1c} ranges, with increases only apparent beyond 5.5%. The relationships between Hb_{A1c} and cause-specific mortalities were similar, with cardiovascular mortality being the strongest.

Comment (NC): This study explored the paradox of the association of low Hb_{A1c} and high mortality seen in some previous observational studies. This was a large nondiabetic population with greater numbers in the lower Hb_{A1c} range compared with previous studies. It did not show an increased mortality at lower Hb_{A1c} and there was a higher mortality with increasing Hb_{A1c} above 5.5%. This certainly makes more sense, and perhaps points to the low event rates at lower Hb_{A1c} values in previous studies.

Reference: Diabetologia 2011 (Online First)
http://www.springerlink.com/content/066l67757q6222k8/

Evidence that nasal insulin induces immune tolerance to insulin in adults with autoimmune diabetes

Authors: Fourlanos S et al

Summary: Patients with recent-onset, noninsulin-dependent type 1 diabetes mellitus (n=52) were randomly allocated to receive nasal insulin or placebo for 12 months in this study; during the study period, there was a 35% decline in β-cell function and 44% of participants progressed to insulin therapy. There were no significant between-group differences for levels of fasting blood glucose, serum C peptide or glucagon-stimulated serum C peptide, but nasal insulin was associated with a significant, sustained blunting of the insulin antibody response to injected insulin. Nasal insulin was also associated with suppression of the interferon-γ response of blood T-cells to proinsulin in a small cohort of participants.

Comment (PL): This study by the highly respected Melbourne group of Harrison and Colman continues their work on the potential of mucosa (intranasal)-mediated immune tolerance in the prevention of type 1 diabetes. Studies of the use of mucosal insulin to prevent diabetes were very successful in mice, and translationally very disappointing in humans. This study examined the potential mechanisms responsible for the failure of such studies, and finds, positively, that the antibody response to SC insulin was suppressed by prior treatment with nasal insulin. However, this did not translate to protection of β-cell function in these adults with established type 1 diabetes. It remains possible that a targeted approach in children may have some efficacy.

Reference: Diabetes 2011;60(4):1237–45
http://diabetes.diabetesjournals.org/content/60/4/1237.abstract

Valsartan improves β-cell function and insulin sensitivity in subjects with impaired glucose metabolism

Authors: van der Zijl NJ et al

Summary: Patients with impaired fasting glucose and/or impaired glucose tolerance received valsartan 320 mg/day (n=40) or placebo (n=39) for 26 weeks in this RCT. β-cell function and insulin sensitivity were assessed with a combined hyperinsulinaemia-euglycaemic and hyperglycaemic clamp, with subsequent arginine stimulation and a 2-hour 75-gram oral glucose tolerance test. Compared with placebo, valsartan was associated with: i) significant increases in both first- and second-phase glucose insulin secretion (p values of 0.028 and 0.002, respectively); ii) a significant increase in the oral glucose tolerance test-derived insulinogenic index (p=0.027); iii) significantly increased clamp-derived insulin sensitivity (p=0.049); and iv) a significant decrease in both systolic and diastolic blood pressure. Enhanced arginine-stimulated insulin secretion did not differ significantly between the two groups, and BMI remained unchanged in both groups.

Comment (PL): Data have been both encouraging and disappointing on the role of anti-angiotensin strategies in the prevention of type 2 diabetes mellitus. This study is an attempt to put some mechanistic understandings under this question. In a medium-sized group of normotensive subjects with impaired glucose metabolism, the angiotensin receptor blocker valsartan improved glucose-stimulated insulin release and insulin sensitivity. It is probably sufficient at this stage to factor in potentially favourable effects on metabolism when treating overweight patients with hypertension with angiotensin receptor blockers, rather than consider a specific use of such agents for the prevention of type 2 diabetes.

Reference: Diabetes Care 2011;34(4):845–51
http://care.diabetesjournals.org/content/34/4/845

Association between passive and active smoking and incident type 2 diabetes in women

Authors: Zhang L et al

Summary: These investigators explored the relationships between exposure to passive and active smoking and type 2 diabetes mellitus risk among the 100,526 women from the Nurses' Health Study who did not have prevalent diabetes in 1982; 5392 incident cases of type 2 diabetes developed during 24 years of follow-up. Among nonsmokers, those with occasional or regular exposure to passive smoke had a greater risk of developing type 2 diabetes than those with no exposure to passive smoke (relative risks 1.10 [95% CI 0.94–1.23] and 1.16 [1.00–1.35], respectively). All ex-smokers had a 28% increased risk of incident type 2 diabetes, and although it decreased as the time since quitting increased, it was still significantly increased 20–29 years after quitting (relative risk 1.15 [95% CI 1.00–1.32]). The relative risks of incident type 2 diabetes among current smokers ranged from 1.39 (95% CI 1.17–1.64) for 1–14 cigarettes per day to 1.98 (1.57–2.36) for ≥25 cigarettes per day (versus nonsmokers with no passive smoke exposure).

Comment (PL): These data from the huge and widely known Nurses study (>100,000 subjects, aged ≥20 years) show an independent and markedly dose-dependent (from passive, to past to active smokers) relationship between cigarette smoking and incidence of type 2 diabetes. The paper noted a study of 600 people who reported never having smoked cigarettes, in which >90% had nicotine metabolites in their urine, highlighting the pervasive nature of passive smoking. The underlying mechanism most likely relates to oxidative stress and inflammation, and by inference, the association between diabetes and cigarette smoking may have been underestimated in the past.

Reference: Diabetes Care 2011;34(4):892–7
http://care.diabetesjournals.org/content/34/4/892

Effect of sitagliptin therapy on postprandial lipoprotein levels in patients with type 2 diabetes

Authors: Tremblay AJ et al

Summary: The effects of sitagliptin on glucose homoeostasis and levels of postprandial lipids and incretin hormone were investigated in 36 patients with type 2 diabetes mellitus who received 6 weeks each of sitagliptin 100 mg/day and placebo in a crossover design with a 4-week washout period. Compared with placebo, sitagliptin was associated with statistically significant differences in the areas under the curves (AUCs) for: i) plasma apolipoprotein (apo)B (–5.1%); ii) apoB-48 (–7.8%); iii) triglycerides (–9.4%); iv) VLDL cholesterol (–9.3%); v) free fatty acids (–7.6%); vi) glucose (–9.7%); vii) plasma intact glucagon-like peptide (+67.8%); viii) glucose-dependent insulinotropic polypeptide (+67.3%); and ix) plasma glucagon (–9.7%). Homoeostasis model assessment index insulin resistance and β-cell function were also improved with sitagliptin therapy versus placebo (–14.6% and +32.3%, respectively). AUCs for plasma insulin and C-peptide were not significantly different between sitagliptin and placebo.

Comment (PL): Postprandial hyperlipidaemia is a prominent feature of diabetes, and it is associated with elevated risk of cardiovascular disease due to the penetration of atherogenic lipoproteins into the vessel wall. Incretins are gut hormones responsible for appreciable postprandial release of insulin, a response that is attenuated in diabetes. The breakdown of incretins is prevented by dipeptidyl peptidase-4 inhibitors such as sitagliptin. Sitagliptin treatment reduced both dietary and endogenously derived levels of circulating atherogenic lipoproteins in association with improved insulin sensitivity and β-cell functions. Multifaceted modifications to the dysmetabolic state of diabetes are obviously preferred in terms of reducing cardiovascular disease risk.

Reference: Diabetes Obes Metab 2011;13(4):366–73
http://onlinelibrary.wiley.com/doi/10.1111/j.1463-1326.2011.01362.x/abstract

