Diabetes Research Review™

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In this issue:

Abbreviations used in this issue:

CABG = coronary artery bypass graft; **CV** = cardiovascular; **GLP** = glucagon-like peptide; **HARP** = Hospital Admission Risk Programme; **HR** = hazard ratio; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention; **TIA** = transient ischaemic attack.

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Welcome to issue 111 of Diabetes Research Review.

The final issue for 2018 begins with research reporting reductions in the risk of macrovascular outcomes among severely obese patients with type 2 diabetes who undergo bariatric surgery. There are also two studies conducted in patients with diabetes from the ASCEND Study Collaborative Group, both of which were published in the same issue of N Engl J Med: one compared the benefits and hazards of aspirin for primary CV prevention, and the other evaluated the impact of increased n-3 fatty acid intake on CV disease risk. Other included research reports on persisting socioeconomic inequalities among hospital admissions for major CV events in UK patients with diabetes, which are likely also seen worldwide.

I hope you have enjoyed your updates in diabetes research this year, and I look forward to returning with more next year.

Kind Regards,

Prof. Peter Little AM

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Association between bariatric surgery and macrovascular disease outcomes in patients with type 2 diabetes and severe obesity

Authors: Fisher DP et al.

Summary: Relationships between bariatric surgery and incident coronary artery disease and cerebrovascular disease events were explored in a retrospective study involving 5301 US patients with type 2 diabetes and BMI ≥35 kg/m^2; 76% of the patients had undergone Roux-en-Y gastric bypass, 17% had undergone sleeve gastrectomy and 7% had undergone adjustable gastric banding. A matched cohort of 14,934 nonsurgical patients served as a control group. Compared with the controls, patients who had undergone bariatric surgery had a lower 5-year incidence of coronary artery or cerebrovascular events (2.1% vs. 4.3%; HR 0.60 [95% CI 0.42–0.86]), driven by a lower incidence of coronary artery disease events (1.6% vs. 2.8%; 0.64 [0.42–0.99]), whereas the incidence of cerebrovascular disease events did not differ significantly (0.7% vs. 1.7%; 0.69 [0.38–1.25]).

Comment: Bariatric surgery has profound effects on metabolism in human subjects, and the effects occur rapidly and before appreciable weight loss. As always, the major issue is dysmetabolism and macrovascular disease and the impact of favourably modulating various metabolic dyscrasias over the longer term. Here the CV fate of some 5000 subjects with type 2 diabetes who underwent bariatric surgery was related to that of 14,000 matched control subjects. Analysis at 5 years postsurgery revealed a 40% reduction in both macrovascular events and coronary artery disease with no difference in cerebrovascular disease. In patients with severe obesity, bariatric surgery needs to be a part of the conversation about its potential role in reducing macrovascular CV events.

Reference: JAMA 2018;320:1570–82

Abstract

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Effects of aspirin for primary prevention in persons with diabetes mellitus

Authors: The ASCEND Study Collaborative Group

Summary: Adults with diabetes but no evident CV disease (n=15,480) were randomised to receive aspirin 100 mg/day or placebo, and were followed for a mean of 7.4 years. Compared with placebo, aspirin recipients had a significantly lower rate of serious vascular events (primary outcome [MI, stroke/TIA or death from any vascular cause, excluding confirmed intracranial haemorrhage]; 8.5% vs. 9.6%; rate ratio 0.88 [95% CI 0.79–0.97]), but a significantly higher rate of major bleeding events (4.1% vs. 3.2%; 1.29 [1.09–1.52]), mostly GI and other extracranial bleeding. There was no significant between-group difference for the incidence of GI tract cancer or any cancer, although longer term follow-up is planned for these outcomes.

Comment: Based on laboratory research, clinical trials and general usage, there is serious competition between aspirin and metformin for the title of drug with the most impact on human health. Aspirin has recently received enormous attention because of the publication of the results of clinical trials. It has been a fascinating evolution of the actions of aspirin in terms of efficacy versus safety and the outcomes in patient cohorts of multiple risk levels. This study looked at the use of low-dose aspirin ('baby aspirin' and I seriously dislike that term) in preventing the first serious vascular event in patients with diabetes but no evidence of CV disease, and covered over 15,000 participants followed for over 7 years. The most reduction in serious vascular events (about 10%) was matched by the high rate of major bleeding events, mostly various types of extracranial bleeding. Possibly the only acceptable outcome would be if it were possible to target aspirin to some cohort with higher vascular risk and lower bleeding risk where the risk-benefit ratio might be tipped in favour of the use of aspirin.

Reference: N Engl J Med 2018;379:1529–39
Abstract

Effects of n-3 fatty acid supplements in diabetes mellitus

Authors: The ASCEND Study Collaborative Group

Summary: Patients with diabetes and no evidence of atherosclerotic CV disease (n=15,480) were randomised to receive n-3 fatty acids 1g or placebo daily in this trial. Mean follow-up was 7.4 years, and the adherence rate was 76%. There was no significant difference between the fatty acid and placebo arms for the first serious vascular event rate (nonfatal MI, nonfatal stroke, TIA or vascular-related death, excluding intracranial haemorrhage; primary outcome; 8.9% vs. 9.2% [p=0.55]), the serious vascular event or revascularisation rate (11.4% vs. 11.5%), the all-cause mortality rate (9.7% vs. 10.2%) or the nonfatal serious adverse event rate.

Comment: There is massive worldwide consumption of fatty acids and modified fatty acids in pure form and in a variety of products. The American Heart Association makes extensive recommendations for the consumption of these products to protect against CV disease (please see R De Caterina, N Engl J Med 2011;364:2439–50 for an excellent review of the area). This was a huge (greater than 15,000 patients) study of the efficacy of 1g capsules containing either n-3 (also called omega-3) fatty acid or matching placebo (olive oil) taken once per day in patients with diabetes but without evidence of atherosclerotic CV disease. Over the considerable average period of 7.4 years, there were serious adverse vascular events in 689 patients (8.9%) in the n-3 fatty acid group and 712 (9.2%) in the placebo olive oil group. These values were not statistically significant (p=0.55). Several other CV measures showed the same outcome. Having diabetes would render this as a high-risk group, and there was no apparent benefit of the consumption of this dose of n-3 (omega-3) fatty acids.

Reference: N Engl J Med 2018;379:1540–50
Abstract

Independent commentary by Professor Peter Little, who is Head of the School of Pharmacy (Pharmacy Australia Centre of Excellence) at the University of Queensland. Peter is a past national President of Diabetes Australia. For full biography please click here.

Sustained socioeconomic inequalities in hospital admissions for cardiovascular events among people with diabetes in England

Authors: Shather Z et al.

Summary: This study sought to identify changes in socioeconomic inequalities among patients aged ≥45 years with diabetes admitted to UK hospitals for major CV causes (acute MI, stroke, PCI and CABG) for the 2004–2005 and 2014–2015 periods. Patients aged ≥65 years accounted for 71% of admissions, and men accounted for 63.3%. There was a steady increase in the number of admissions across deprivation quintiles, with individuals from the most versus least deprived quintile having a 1.94-fold increased risk of acute MI (95% CI 1.79–2.10), a 1.92-fold increased risk of stroke (1.78–2.07), a 1.66-fold increased risk of requiring CABG (1.50–1.74) and a 1.76-fold increased risk of requiring PCI (1.64–1.89). There was no significant difference between the least and most deprived quintiles for absolute differences in the acute MI rate (p=0.29), but the rates were significantly reduced by 17.5, 15, and 11.8 per 100,000 for stroke, CABG and PCI, respectively (p≤0.01).

Comment: This study in the UK looked at the relationship between socioeconomic status and CV disease in patients hospitalised for diabetes. One might think that the UK is a suitable place to undertake such a study, but the impact of socioeconomic status on health is probably a worldwide phenomenon. The study was over two periods 10 years apart. The data showed that hospital admissions for diabetes-related major CV events showed a marked socioeconomic gradient with higher admission rates with increasing socioeconomic deprivation. The data indicate that there is inadequate attention to social factors in the generation and application of health policies on a nationwide basis, and policy needs to be modified to reduce inequalities in diabetes outcomes.

Reference: Am J Med 2018;131:1340–8
Abstract

Successful treatment of prediabetes in clinical practice using physiological assessment (STOP DIABETES)

Authors: Armato JP et al.

Summary: This retrospective observational study assessed a real-world, pathophysiology-based therapeutic approach for type 2 diabetes prevention in 422 evaluable at-risk individuals. High-risk individuals received metformin, pioglitazone, a GLP-1 receptor agonist and lifestyle therapy, while intermediate-risk individuals received metformin, pioglitazone and lifestyle therapy; those who refused pharmacological therapy received lifestyle therapy. Mean follow-up was 32.09 months. Compared with participants who received lifestyle therapy only, those who received metformin, pioglitazone and lifestyle therapy with and without a GLP-1 receptor agonist had lower rates of progression to type 2 diabetes (0% and 5%, respectively, vs. 11%; adjusted HRs 0.12 [95% CI 0.02–0.94] and 0.29 [0.11–0.78]). The strongest predictor of type 2 diabetes prevention was an improvement in β-cell function.

Comment: One of the intriguing early observations in the prediabetes and prevention of progression area was that if you took a group of people with prediabetes and assessed them sometime later, then one-third stayed as prediabetes, one-third progressed to diabetes and one-third returned to normal – this occurred when prevailing dogma was that diabetes was a progressive disease with a natural history that could not be stopped. However, landmark studies have shown that the progression from prediabetes to diabetes can be arrested by lifestyle interventions and medical therapy. This American study of 2000 individuals assessed if "*real-world, pathophysiology-based, therapeutic approach could prevent development of type 2 diabetes in high-risk individuals*". Compared with lifestyle therapy, drug therapy reduced the risk of people progressing to diabetes in a 3-year period by about 80%. Metformin, pioglitazone and GLP-1 agonists were the drugs used. Mechanistically, improved β-cell function was the strongest predictor for preventing progression. Considering the devastating complications of diabetes, serious consideration needs to be given as to how early medical intervention should occur.

Reference: Lancet Diabetes Endocrinol 2018;6:781–9
Abstract

Differences in health outcomes associated with initial adherence to oral antidiabetes medications among veterans with uncomplicated type 2 diabetes

Authors: Gatwood JD et al.

Summary: The impact of oral antidiabetes medication adherence over a 5-year period on macrovascular and microvascular complications, time to insulin therapy, revascularisation, admissions and death was explored in a retrospective cohort of 159,032 US veterans with uncomplicated diabetes. Individuals who were initially nonadherent to oral antidiabetes therapy over 5 years of treatment had higher likelihoods of MI (HR 1.14 [95% CI 1.03–1.27]), ischaemic stroke (1.22 [1.05–1.42]) and death (1.21 [1.15–1.28]), and those whose adherence was <20% during the first year had particularly high risks of ischaemic stroke (1.78 [1.27–2.49]) and death from any cause (1.33 [1.17–151]). Individuals who were adherent had higher likelihoods of microvascular complications and chronic kidney disease.

Comment: Adherence to drug therapy is a classic area of miscomprehension by health professionals versus the real-life situation. The current paper studied the health outcomes of military veterans in the US as a 5-year survival analysis for type 2 diabetes. Not surprisingly, people who were nonadherent had higher rates of MI and ischaemic stroke and a 21% higher mortality rate. The authors naïvely stated that *"adherence is paramount to disease management and this should be stressed…"* etc, etc – as if people actually choose not to be adherent. Adherence is a major area of research in pharmacy and psychology, and it is a very complicated subject. The bottom line is that the complexity of the factors effecting and determining adherence to medications should be appreciated and 'you must take your medication' is probably not a sufficient intervention to move the adherence profile appreciably upward. Please see Mathes T et al. 'Adherence influencing factors – a systematic review of systematic reviews.' Arch Public Health 2014;72:37.

Reference: Diabet Med 2018;35:1571–9
Abstract

Utility of the Hospital Admission Risk Programme diabetes risk calculator in identifying patients with type 2 diabetes at risk of unplanned hospital presentations

Authors: McGrath RT et al.

Summary: The HARP (Hospital Admission Risk Programme) diabetes risk tool was evaluated for its ability to predict which patients with type 2 diabetes are likely to require an unplanned hospital presentation among a retrospective cohort of 278 patients; 67.3% were classified as low risk, 32.7% were classified as medium risk and no patients were classified as high or urgent risk. A medium HARP score increased the risk of unplanned hospital presentations over the subsequent 12-month period by a factor of 3.1 (95% CI 1.35–7.31]) after adjustments for confounders. Compared with patients who did not present to hospital, those who did had significantly higher part A scores (14.2 vs. 11.4 [p=0.034]); there was no significant between-group difference for part B scores (p=0.860).

Comment: It is good to be able to review an Australian paper and this one is from the Department of Diabetes at the Royal North Shore Hospital in Sydney. Prevention of readmission to hospital is currently one of the top order areas of interest of hospital administrators and health departments. Multiple risk assessment tools have been developed, and this study used HARP, a tool for calculating the risk of unplanned hospital visits by people with type 2 diabetes. The tool includes a clinical assessment component and a psychosocial and self-management impact score. In a substantial study of almost 300 patients (average age 65 years and duration of diabetes of 11 years), the HARP scores were associated with an over 3-fold increased risk of unplanned hospital admission. Interestingly, the clinical assessment scores were considerably more useful in practice than the part B psychosocial and self-management impact scores. Clearly, the range of data supporting our understanding of factors affecting hospital readmissions is expanding and making for better informed decisions about likely prognosis.

Reference: Intern Med J 2018;48:1198–205
Abstract

LeucoPatch system for the management of hard-to-heal diabetic foot ulcers in the UK, Denmark, and Sweden

Authors: Game F et al., for the LeucoPatch II trial team

Summary: Patients with diabetes and a hard-to-heal foot ulcer, for which the area affected remained >50% after a 4-week run-in, were randomised to prespecified good standard care with (n=132) or without (n=137) weekly application of LeucoPatch, a device that uses bedside centrifugation without additional reagents to generate a disc comprising autologous leucocytes, platelets and fibrin. An intent-to-treat analysis revealed that compared with standard care alone, the use of the LeucoPatch device was associated with a higher rate of ulcer healing at 20 weeks (primary outcome; 34% vs. 22%; odds ratio 1.58 [96% CI 1.04–2.40]) and a significantly shorter time to healing (p=0.0246), with no difference in adverse events. The most common serious adverse event was diabetic foot infection, for which there were 24 and 20 events in the LeucoPatch and standard care groups, respectively. No device-related adverse events were recorded.

Comment: Diabetic foot ulcer arising mostly from the compromised blood circulation associated with the vascular damage caused by hyperglycaemia, and the negative impact of hyperglycaemia on wound healing, is one of the most insidious and debilitating but least well treated complications of diabetes worldwide. Aggressive treatments involve the use of growth factors and immune cells to promote wound healing. Generally, modulation of the immune system by drugs, cytokines and immune cells directly is emerging as a very promising pathway to address hitherto difficult-to-treat conditions. This was a trial of a commercial product known as LeucoPatch. The product comes from a Danish company and the study was conducted in the UK. The product resulted in improved healing of difficult foot ulcers. I'm not aware that the product is available in Australia, but the study points to the emerging products for use in the treatment of foot ulcers in people with diabetes.

Reference: Lancet Diabetes Endocrinol 2018;6:870–8
Abstract

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