Diabetes & Obesity
RESEARCH REVIEW™

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Issue 148 – 2021

In this issue:

Abbreviations used in this issue
CV = cardiovascular
DKA = diabetic ketoacidosis
DPP = dipeptidyl peptidase
HbA_{1c} = glycosylated haemoglobin
HHS = hyperglycaemic hyperosmolar state
HOMA-IR = homeostatic model assessment of insulin resistance
SGLT = sodium glucose cotransporter

Welcome to issue 148 of Diabetes and Obesity Research Review.

It has been over 12 months since the whole country has been in a level 4 lockdown, so I thought I would review some of the literature on COVID-19 and diabetes that has been published in that time. Not surprisingly, there has been an enormous number of publications on COVID-19, which are of variable quality, and I have tried to pick out a few that are of greatest interest and relevance; however, there were very few papers specifically related to the delta variant and diabetes.

Thank you for your comments and feedback, which we greatly appreciate. Please keep them coming.

Best regards,

Professor Jeremy Krebs
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Diabetes-related acute metabolic emergencies in COVID-19 patients

Authors: Papadopoulos VP et al.

Summary: This was a systematic review with meta-analysis of 44 studies describing the clinical profiles, outcomes and mortality rates with respect to patients with COVID-19 and DKA, HHS (hyperglycaemic hyperosmolar state), both or euglycaemic DKA. Factors significantly, independently predictive of death were COVID-19 requiring ICU admission, DKA/HHS and acute kidney injury, and factors significantly predictive of DKA/HHS were increased COVID-19 severity, elevated lactate level, increased anion gap and acute kidney injury. SGLT-2 inhibitor use was significantly associated with euglycaemic DKA and significantly negatively associated with acute kidney injury. The combined mortality across case series, cross-sectional studies and meta-analyses was 27.1%, although heterogeneity was considerable.

Comment: We have known since the early months of the pandemic that having diabetes was associated with worse outcomes if a person became infected with COVID-19. This systematic review and meta-analysis examined associations between acute metabolic emergencies and outcomes, specifically DKA and HHS. It makes the point that the lines between the two are often blurred, and that with SGLT-2 inhibitors increasing the risk of euglycaemic DKA, the situation is even further complicated. However, the overall message is clear that people with diabetes presenting with COVID-19 and a metabolic emergency have very high mortality. This is particularly true if there is a need for mechanical ventilation, simultaneous DKA and HHS, and if there is co-existing acute kidney injury, which is notably relatively protected for by SGLT-2 inhibitors.

Reference: Diabetol Int; Published online March 23, 2021
Abstract

Independent commentary by Professor Jeremy Krebs MBChB, FRACP, MD

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. **FOR FULL BIO CLICK HERE.**

Telemonitoring, telemedicine and time in range during the pandemic: paradigm change for diabetes risk management in the post-COVID future

Authors: Danne T et al.

Summary: These authors conducted a critical review of reports on telemonitoring in acute hospitalised patients with diabetes and during their daily diabetes management. Indications and implications of adopting telemonitoring and telemedicine in the current climate and for the future were also discussed. They note that despite restricted access to standard clinical care during the COVID-19 pandemic, there has been no evidence of deterioration in glycaemic control for patients with type 1 diabetes who use telemonitoring of glucose level data. Use of telemonitoring and initiation of glucose-lowering treatment immediately following admission were both noted as measures to mitigate the increased risk of severe COVID-19 for patients with diabetes admitted to hospital. Also, routine telemonitoring can be used to help identify patients with diabetes who are likely to require in-person consultation and care and also those who may be successfully managed with telemedicine. They also note that the unmet need for wider application of telemedicine and telemonitoring via continuous glucose monitoring for individuals with diabetes has been highlighted by the COVID-19 pandemic.

Comment: In addition to the use of glucose sensors for data collection, there is also the issue of utility of that information for patients and also their healthcare providers. In the setting of a lockdown with limited face-to-face clinical interactions, we have become accustomed to the use of telephone or Zoom consultations. However, there is also the remote transmission of data from sensors and/or pumps, which further augment these interactions. This is all in the realm of telemedicine. This review discusses this and the potential benefits that it may bring. For me it highlights a number of issues that we have yet to grapple with in NZ. The first and perhaps most important is the access to technology for patients. This applies to pumps and sensors. The second is the technology literacy for both patients and healthcare professionals alike, to be able to utilise the benefits of the devices. The third is the structure of the healthcare system to enable and facilitate, but also limit and optimise, the use of this type of telemedicine approach. I don't think we have even begun to address the third issue, and in a staff-constrained and stressed system we must. Figure 1 in this paper is a useful summary of risks for people with diabetes and COVID.

Reference: Diabetes Ther; Published online Aug 2, 2021
Abstract

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Impact of COVID-19 lockdown on flash and real-time glucose sensor users with type 1 diabetes in England

Authors: Navis JP et al.

Summary: Differences in sensor-based outcomes before and during lockdown periods were explored for a UK cohort of 269 patients who used Freestyle Libre or Dexcom G6 glucose sensors for managing their type 1 diabetes. Compared with before lockdown, glucose level time in range of 3.9–10mM was significantly increased 2 and 3 weeks into lockdown in patients with >70% sensor use (59.6% and 59.3%, respectively, vs. 57.5% [p values 0.002 and 0.035]), with greater proportions of patients achieving ≥70% time in range (27.8% and 30.5% vs. 23.3%). Dexcom G6 users (n=79) had a significantly lower percentage of time below range of <3.9mM compared with Freestyle Libre users (n=190) during lockdown (1.8% and 1.4% at weeks 2 and 4, respectively, vs. 4% [p<0.005 for both]).

Comment: The impact of a lockdown on diabetes management is of interest. There are many factors that might come in to play, such as change of routine with respect to work, food, exercise and daytime patterns, as well as a focus on diabetes management due to fear of outcome if contracting COVID. This paper reports metrics of glycaemic management for those using glucose sensors in the UK during their lockdown. They observed modest improvements in control compared with pre-lockdown. We can't conclude whether that would also apply to those using finger-prick capillary monitoring, but it is an encouraging sign.

Reference: Acta Diabetol 2021;58:231–7
Abstract

COVID-19 in a country with a very high prevalence of diabetes: the impact of admission hyperglycaemia on mortality

Authors: Martínez-Murillo C et al.

Summary: These researchers reported on diabetes and hyperglycaemia for 480 patients admitted for COVID-19 in Mexico; admission hyperglycaemia was present in 48.5% of the patients, and of these, 29% had pre-existing diabetes. Patients with admission hyperglycaemia had an increased requirement for invasive mechanical ventilation, higher urea levels, higher D-dimer levels, higher neutrophil-lymphocyte ratios and lower lymphocyte counts. Admission hyperglycaemia was associated with invasive mechanical ventilation, and D-dimer level was associated with glucose level. Factors associated with increased mortality risk were age ≥50 years (odds ratio 2.09 [95% CI 1.37, 3.17]), pre-existing diabetes (2.38 [1.59, 5.04]) and admission hyperglycaemia (8.24 [4.74, 14.32]).

Comment: There have been a number of reports highlighting the possibility that there may be a bidirectional interaction between COVID-19 and diabetes. By that, I mean that we have clear evidence that having pre-existing diabetes increases the risk of a poor outcome with COVID-19, but there is also emerging evidence that COVID-19 might be related to the development of diabetes. The latter may be no more than the association that we commonly see with infection or other metabolic stress, which in a person with a predisposition to type 2 diabetes is enough to trigger hyperglycaemia. However, there may be more to it, which will emerge with time. Nevertheless, this paper from Mexico, a country with a very high rate of obesity and type 2 diabetes, reports hyperglycaemia in almost 50% of people admitted to hospital with COVID-19. Once again, this was strongly related to mortality.

Reference: Endocrinol Diabetes Metab 2021;4:e00279
Abstract

COVID-19 and diabetes mellitus: from pathophysiology to clinical management

Authors: Lim S et al.

Summary: The authors of this review focus on clinical recommendations for patients with diabetes who are at risk of or affected by COVID-19. They note that although ACE (angiotensin-converting enzyme)-2 is the main entry receptor for the virus and DPP-4 might also be a binding target, preliminary data have not shown DPP-4 inhibitors to have a notable impact. They also note that SGLT-2 inhibitors cannot be recommended due to their propensity to cause adverse effects in patients with COVID-19 because of their pharmacological properties. Therefore, insulin should currently be the primary approach for controlling acute glycaemia. They also note that although most available evidence is for type 2 diabetes (due to its greater prevalence), limited evidence is now available for type 1 diabetes in the setting of COVID-19. The authors also advise that most of their conclusions are preliminary, and further investigation into the optimal management of diabetes in the setting of COVID-19 is warranted.

Comment: This is a pretty comprehensive paper that outlines the state of knowledge as at November 2020 on many of the issues related to the interaction between diabetes and COVID. Figure 4 of this paper is useful as a reminder to us about which glucose-lowering medications people with diabetes may be taking and how these should be reviewed depending on their individual situation. Now that we have access to SGLT-2 inhibitors, this becomes very relevant. Although they may have some protective effects with regards to acute kidney injury, the balance of risks favours discontinuation in anyone who has COVID, and therefore probably anyone who is symptomatic and awaiting the result of a test.

Reference: Nat Rev Endocrinol 2021;17:11–30
Abstract

Post COVID-19 syndrome ('long COVID') and diabetes: challenges in diagnosis and management

Authors: Raveendran AV & Misra A

Summary: These authors reviewed published literature on 'post-COVID-19 syndrome', or 'long COVID', in patients with diabetes. They found that post-COVID-19 symptoms can be secondary to organ dysfunction, the effects of hospitalisation and drugs, and also unrelated to these. A bidirectional relationship between type 2 diabetes and COVID-19 was evident. A variety of pathophysiological mechanisms associated with the presence of diabetes was also shown to influence post-COVID-19 syndrome. In patients with diabetes, COVID-19 was found to have an additive or exacerbatory effect on tachycardia, sarcopenia (and muscle fatigue) and microvascular dysfunction (and organ damage).

Comment: We are beginning to hear more about so-called 'long COVID' or 'post-COVID syndrome'. Because we have not had COVID in NZ to any significant extent, none of us really have any experience in the spectrum of clinical manifestations of acute COVID, let alone long COVID. This paper gives some useful context to this, including a breakdown of several subtypes of long COVID in Table 1. One type is what we commonly see with other viruses causing a chronic fatigue syndrome, but there are also other forms that appear to be distinct. Unfortunately, it would appear that having diabetes may be a risk factor for the development of long COVID as it is for other COVID-related morbidity. The paper also again highlights the emerging evidence of the bidirectional flow between COVID and diabetes.

Reference: Diabetes Metab Syndr 2021;15:102235
Abstract

Diabetes, COVID 19 and mucormycosis: clinical spectrum and outcome in a tertiary care medical center in Western India

Authors: Mishra Y et al.

Summary: The authors of this descriptive study reported on the clinical spectrum and outcomes of COVID-associated mucormycosis ('black fungus') among 953 patients hospitalised for COVID-19 at a single centre in India; the incidence of COVID-associated mucormycosis was 3.36%. Among patients with COVID-associated mucormycosis, 87.5% had diabetes as their most common comorbidity, and most patients had poor glycaemic control (mean HbA_{1c} level 9.06%). Prior exposure to high-dose corticosteroids was documented for 93% of the overall study population. The mortality rate for patients with COVID-associated mucormycosis over the study period (April 12, 2021 to May 31, 2021) was 12.5%.

Reference: Diabetes Metab Syndr 2021;15:102196
Abstract

Post-COVID mucormycosis in India: a formidable challenge

Authors: Rao V et al.

Summary: These researchers explored risk factors for mucormycosis following COVID-19 for 28 patients (22 males) presenting for oral and maxillofacial surgery in India; two of the patients had been vaccinated against COVID-19. Diabetes was a major comorbidity affecting all but one of the patients, including 19 with uncontrolled diabetes. Thirteen patients received steroid therapy (>10 days in four patients), 17 received oxygen and one required ventilator support. The time between COVID-19 recovery and first report of mucormycosis was 10–14 days for eight patients and >15 days for ten patients. Mucormycosis pansinusitis and maxillary osteomyelitis were seen in half the patients.

Reference: Br J Oral Maxillofac Surg; Published online June 28, 2021
Abstract

Comment: These two papers highlight a potential new problem associated with COVID-19, and perhaps greater risk for those with diabetes and particularly now with the delta variant. In normal circumstances, mucormycosis is very rare but very serious, and people with diabetes are at greater risk. These reports from India have suggested that with COVID, the risk of mucormycosis may be much greater – something to be aware of but not panic about. There is much more to be learned about this observation and what the risk factors and potential mitigations are. And now for some non-COVID papers…

Association of cycling with all-cause and cardiovascular disease mortality among persons with diabetes

Authors: Ried-Larsen M et al.

Summary: Associations between time spent cycling and all-cause and CV-related mortality were explored for a prospective cohort of 7459 adults with diabetes from the EPIC study. There were 1673 deaths from all causes over 110,944 person-years of follow-up, and in an analysis of change in time spent cycling, there were 975 deaths over 57,802 person-years of follow-up. Compared with participants who reported no cycling at baseline, those reporting 1–59, 60–149, 150–299 and ≥300 minutes per week had lower risks of death from any cause (respective adjusted hazard ratios 0.78 [95% CI 0.61, 0.99], 0.76 [0.65, 0.88], 0.68 [0.57, 0.82] and 0.76 [0.63, 0.91]). Compared with participants reporting no cycling at both baseline and 5-year examinations, the risk of all-cause mortality was not significantly reduced for those who cycled and then stopped (adjusted hazard ratio 0.90 [95% CI 0.71, 1.14]), but it was for those who initially did not cycle but then started (0.65 [0.46, 0.92]) and those who reported cycling at both examinations (0.65 [0.53, 0.80]). The results for CV-related mortality were similar.

Comment: Finally, the paper that proves me right. I'm a passionate road cyclist and not many days do not start with at least a 30km ride. More than anything it clears my mind and gives me time to plan the day. This paper, which is an analysis of the large EPIC prospective epidemiological study, examined the association between cycling and CV-related mortality in people with diabetes. The effect of cycling was protective, both for those who regularly cycled and those who took it up. Most importantly, it was independent of other forms of exercise. What can I say. On ya bike. The Krebs cycle in action…

Reference: JAMA Intern Med; Published online July 19, 2021
Abstract

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Capillary ketone concentrations at the time of colonoscopy

Authors: Hamblin PS et al.

Summary: These Australian researchers sought to determine a nondiabetic reference interval for capillary ketone levels at the time of colonoscopy using data from an observational study of patients with type 2 diabetes treated with (n=37) and without (n=105) SGLT-2 inhibitors and a reference population of 151 normoglycaemic individuals. The median capillary ketone level measured <90 mins prior to colonoscopy for the reference population was 0.4 mmol/L and the respective levels for patients with diabetes receiving and not receiving SGLT-2 inhibitors were 0.3 and 0.5 mmol/L. A greater proportion of diabetics receiving SGLT-2 inhibitors had a capillary ketone level >1.0 mmol/L compared both with their counterparts not receiving SGLT-2 inhibitors and with the reference group (24% vs. 5% and 9%, respectively [p<0.05]); there was also a significantly greater proportion with a level >1.5 mmol/L compared with the diabetics not receiving SGLT-2 inhibitors but not compared with the reference group (11% vs. 1% [p<0.05] and 5%). It was concluded that the upper limit of the range for capillary ketone levels in normoglycaemic individuals (1.7 mmol/L) was relevant for assessing patients with diabetes treated with SGLT-2 inhibitors at the time of colonoscopy.

Comment: With the availability of SGLT-2 inhibitors, we are all feeling our way with safe prescribing. The main adverse effect of concern is the risk for euglycaemic ketoacidosis. Whilst it is uncommon, it is very serious. As I am sure many of you will be aware, we have already had a number of presentations to hospital with euglycaemic DKA in people on SGLT-2 inhibitors in Wellington. There are several situations where the risk of this occurring is greater, and the NZSSD have published guidance on this together with the Australian Diabetes Society. This is available on the NZSSD website. One of the controversial settings is in those undergoing colonoscopies. In this situation, because of the low carbohydrate bowel preparation and fasting prior to the procedure, many people without diabetes will develop low levels of ketones and are not at risk of significant DKA. This makes producing hard and fast guidelines difficult and highlights how important it is to assess every person individually. This paper gives some very interesting summary data on this situation. The NZSSD guideline will be updated accordingly over the coming weeks.

Reference: Diabetes Care 2021;44:e124–6
Abstract

Association of insulin resistance and type 2 diabetes with gut microbial diversity

Authors: Chen Z et al.

Summary: Associations of gut microbiome composition with insulin resistance and type 2 diabetes were explored in two prospective population-based cohorts from the Netherlands, namely the Rotterdam Study (n=1418) and the LifeLines-DEEP study (n=748), in which there were 193 cases of type 2 diabetes overall. Associations were seen of lower microbiome Shannon index and richness with higher HOMA-IR, and patients with versus without type 2 diabetes had reduced richness (odds ratio 0.93 [95% CI 0.88, 0.99]). There was also a significant association between β diversity and insulin resistance in both cohorts. Twelve bacterium groups were significantly associated with HOMA-IR or type 2 diabetes. Generally, higher microbiome α diversity and enrichment of butyrate-producing gut bacteria were associated with less type 2 diabetes and lower insulin resistance among individuals without diabetes.

Comment: Are we what we eat? Or are we what our bacteria eat? There's a question for lockdown. There is continued interest in the relationship between our gut microbiome and metabolic health, particularly the risk of type 2 diabetes. It seems to me that for every paper that shows an association or some change in microbiome with an intervention linked to weight or diabetes risk, there is another contradictory paper or negative trial. There is some compelling evidence of associations between the microbiome and metabolism, but whether there is causality remains to be defined. This paper is another to show associations, here between diversity and specific bacterial properties related to production of butyrate, and insulin resistance. Once again, this is intriguing and plausible. Watch this space while you keep following that Mediterranean dietary pattern, including the lockdown glass of red wine.

Reference: JAMA Netw Open 2021;4:e2118811
Abstract

Utilization of telehealth for outpatient diabetes management during COVID-19 pandemic: how did the patients fare?

Authors: Wong V W et al.

Summary: The retrospective records of patients with diabetes who underwent telehealth management in 2020 at two Sydney hospitals (n=994) were compared with those from 12 months earlier when patients attended face-to-face consultations (n=959). The telehealth consultation attendance rate in 2020 for the diabetes services was 88.9%, compared with 85.2% in 2019 (p=0.016). Of the patients reviewed by the same service over the two periods (n=629), improved glycaemic control was seen in 2020 compared with 2019 as evidenced by a lower HbA_{1c} level (62 vs. 66 mmol/mol, or 7.8% vs. 8.2% [p<0.001]), with no significant between-year difference for the number of unplanned admissions (9.2% vs. 11.9% [p=0.100]).

Comment: Here is more on telehealth from closer to home, in Sydney. This paper reviewed the utilisation of telehealth consultations in urban hospital diabetes clinics in Sydney in 2020 during the COVID pandemic, and compared these with face-to-face appointments during the previous year. Of note, there was a small but significantly greater attendance rate with telehealth appointments, and there was also a small but significant improvement in mean glycaemic control. This did not translate to fewer unplanned hospital admissions. There are many factors that come into this, but the main message is that delivering diabetes care by telehealth appears to be a viable option in a system that is very similar to NZ. There are many questions that remain unclear, such as whether all consultations can be via telehealth, whether selected individuals achieve better outcomes with one or other form of appointment, and whether the enthusiasm for and timely attendance with telehealth appointments continues over time and especially out of lockdowns. These aside, it is clear that telehealth is another way we can safely engage with our patients and may be preferable for some.

Reference: Intern Med J; Published online July 6, 2021
Abstract

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