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Case study 3

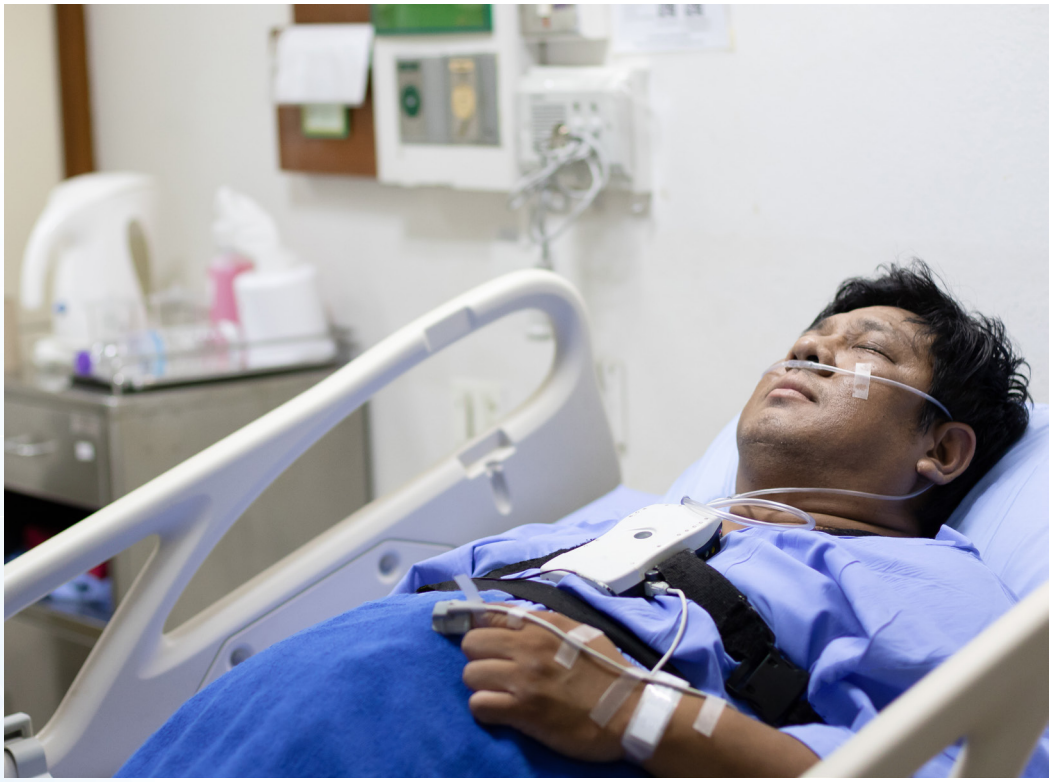
A diabetic patient with COVID-19

This report is a summary of a webinar presentation by Dr Lombard, 22 September 2020.

How would you manage a diabetic patient with COVID-19?

Case 3 – Mr AB, poorly controlled type 2 diabetes mellitus (T2DM)

- 36-years-old, diagnosed with T2DM at age 30 years
- Hypertension, dyslipidaemia, smokes 40+ cigarettes daily, morbidly obese
- Consulting for assessment of severe insulin resistance as he is using huge amounts of insulin (> 200 u/day), severe sensory peripheral neuropathy
- Weight: 125 kg, height: 177 cm, BMI: 40 kg/m^2
- Detailed conversation about diet, smoking and weight loss
- Added pioglitazone 30 mg/day, adjusted insulin, insulin lispro premix 25 u tid, metformin 1 g bd, rosuvastatin 10 mg/day
- Biochemistry - U&E: normal, eGFR: > 90 ml/min/1.73 m^2, HbA_{1c}: 10.0%, clear for protein, LDL: 3.0 mmol/l, HDL: 0.8 mmol/l, TSH: 1.45 mIU/l.



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Dr Lombard's clinical approach

My clinical strategy at this stage was to reduce the insulin dose and regain glucose control. I prescribed 30 mg pioglitazone a day and put him on an insulin lispro premix 25 u three times a day, making the total doses approximately 140 u a day. Still on full-dose metformin, and rosuvastatin 10 mg. His biochemistry then showed a normal U&E, eGFR > 90 ml/min/1.73 m^2, HbA_{1c} 10%. His urine test was clear for proteinuria. He had dyslipidaemia, but his TSH level was normal.

Case 3 continued – 10 years later

- He disappeared for 10 years before returning with worsened health, now diabetic for 16 years
- Still high insulin user, still smoking 40/day
- Gained a lot of weight, now 163 kg; also has pitting oedema
- HbA_{1c}: 9.3%, eGFR: 54 ml/min/1.73 m^2, protein:creatinine ratio: 5.1 mg/mg (nephrotic range), LDL: 2.6 mmol/l, HDL: 0.9 mmol/l
- Fluid retention a problem
- ***What should we do now?***

At the time of this visit three years ago, I had not seen him for 10 years. He was still a high insulin user and still smoking 40 cigarettes a day. He now weighed 163 kg, with marked pitting oedema, and I wondered how much of this was fluid. His HbA_{1c} of 9.3% was not a lot better than previously. His eGFR had dropped from > 90 ml/min/1.73 m^2 to 54 ml/min/1.73 m^2. His protein:creatinine ratio showed nephrotic-range proteinuria, probably contributing to the pitting oedema that was seen in the fluid retention. It was surprising that his LDL of 2.6 mmol/l was not higher in the presence of nephrotic-range proteinuria. The fluid retention was a huge problem: contributing factors include pioglitazone, the nephrotic-range proteinuria, a decreased eGFR and high doses of insulin. At that stage combination insulin had become available, so he was prescribed an insulin degludec and insulin aspart combination, 60-70 u with the evening meal, to which I added insulin lispro premix 50 u, giving more short-acting insulin with the other two meals of the day. Overall, he was using approximately 180 u of insulin. I also added liraglutide and we tried to titrate this to a dose of 1.8 mg, as he could afford it. I withdrew the pioglitazone as I was a bit concerned that it was contributing to the fluid retention. The problem then arose that he lost glucose control, and so we had to reintroduce pioglitazone at 30 mg daily. He was on telmisartan, and I added spironolactone to reduce the fluid retention.

This man was facing inevitable renal failure within 5-6 years, highlighting the dangers of his not having taken care of himself over the preceding 10 years. Having lost those 10 years, it's impossible to make a comeback, regardless of what treatments clinicians attempt.

Case 3 continued – now with regular 4-6-monthly follow-up

- Checking eGFR every 6-8 weeks
- Weight still a huge problem; considering bariatric surgery
- Stress ECG done, very poor effort tolerance (three minutes)
- Referred for angiography: significant coronary artery disease, several stents inserted
- HbA_{1c} now well controlled in the 7-8% range, mostly about 7.5%
- LDL: < 2 mmol/l
- Proteinuria remains high at 5-7 g/day
- eGFR keeps slipping gradually as expected: 55 to 50 to 45, reaching 35 ml/min/1.73 m^2 in August 2019.

So now he was quite scared because I tend to talk straight with my patients and give them the facts. He was now seeing me for regular 4-6-monthly follow-ups, and I was checking his eGFR every 6-8 weeks. His weight was still a huge problem and he was considering bariatric surgery.

I was not happy with the risk profile, poor glycaemic control and smoking. I referred him to cardiology for angiography. He received several stents in his left anterior descending artery and was then put on anti-platelet agents. Now he also had confirmed ischaemic heart disease, which would have made bariatric surgery riskier. His HbA_{1c} was fairly well controlled, remembering that he was on high volumes of insulin. His HbA_{1c} target was 7.5% and now achievable. He made some lifestyle changes with his LDL now at target (< 2 mmol/l). His proteinuria stayed at about 5-7 g/day. His eGFR kept gradually slipping, and he reached 35 ml/min/1.73 m^2 in August 2019. At this stage, I had already added dapagliflozin (off-label) to try to protect the kidneys and reduce both the insulin requirements and body weight. This worked to good effect; the patient felt better and had less fluid retention. It perhaps slowed the eGFR decline but the effect was not impressive.

Case 3 continued – now with very regular follow-up

- Metformin XR reduced to 1 g/day
- Using 160 u insulin per day
- Furosemide plus low-dose spironolactone
- Rosuvastatin 40 mg/day
- Dapagliflozin (off-label!!)
- Proteinuria reduced to 2.5 g/day
- Hoping to slow the decline in eGFR.

My feeling was that we could have definitely bought him several more years and had he been in a better position, maybe he would have survived he COVID-19 infection

I replaced the torasemide with furosemide, because furosemide is better with regard to potassium. He was on a very low dose of spironolactone because of the risk of hyperkalaemia. Rosuvastatin had been increased to 40 mg and he continued to take dapagliflozin, which did reduce his proteinuria to 2.5 g/day from 7 g/day.

Case 3 – the final chapter

- June 2020: reports dizziness, blood pressure 114/62 mmHg – too low for renal patient
- Had finally stopped smoking about 40 days previously
- eGFR 20 ml/min/1.73 m^2!! Hoped this was all blood pressure-related
- Planned to see him six weeks later and undertake blood tests in two weeks
- Stopped metformin, reduced pioglitazone to 15 mg
- Wife phoned; he was admitted to hospital with COVID-19 infection
- Ended up on ventilation and haemodialysis
- Died about two weeks later after long stay in ICU.

My feeling was that we could have definitely bought him several more years and had he been in a better position, maybe he would have survived the COVID-19 infection. This illustrates the seriousness of complicated diabetes.

What is the evidence for COVID-19 outcomes in relation to T2DM?

Diabetics with COVID-19 infection are at greater risk of a poor outcome, especially those who are poorly controlled; they have a 300-400% increased risk of dying. This is an additional motivation for diabetes patients to ensure they are well controlled, because this will lower their risk of dying from COVID-19.

There are many questions about why T2DM patients do so badly, and why many people develop new-onset diabetes when they get COVID-19. There are many theories; my impression is that the cytokine storm caused by COVID-19 escalates the significant cytokine reactions that are already present in the intra-abdominal fat tissue of those with

T2DM, as well as (probably) in the blood vessel walls. This well-known component of inflammation in T2DM is then worsened by COVID-19. In addition, hypercoagulation may lead to development of clots in the lungs, which often leads to a poor outcome. T2DM patients should therefore be assessed immediately if they become infected with COVID-19 and hospitalised if necessary.

Managing oral antidiabetic agents and COVID-19 infection

If you need to manage patients with diabetes and COVID-19, you must distinguish between mild and severe COVID-19 disease (Figure 12).[1,2] With mild COVID-19 disease, the general practitioner may wonder if they should change the diabetic strategy; there are no concerns regarding the use of metformin and DPP-4 inhibitors, and the use of thiazolidinediones is probably not a concern. Sulphonylureas are also unlikely to be of concern, but patients must continue to monitor their glucose. It is probably safe to continue with SGLT-2 inhibitors, although this is probably the riskiest drug as it increases the risk of diabetic ketoacidosis, which can easily develop with only mild symptoms and mildly elevated glucose.

If severe COVID-19 disease symptoms occur, where the patient is short of breath, is on oxygen and admitted to hospital, I would probably stop all of these medications and admit the patient to the ICU. There is often a huge escalation in insulin requirements in these patients, due to the cytokine storm and inflammation related to COVID-19 infection. It has also been shown that if a patient presents at the hospital with very high glucose levels, even if previously undiagnosed with diabetes, it correlates significantly with a poor outcome.

	Article type	Study population	Prevalence of diabetes	Parameter	Outcome	Risk
Williamson *et al*	Cohort Study	17 425 445*	10%	$HbA_{1c} \geq 58$ mmol/mol (7.5%)	Mortality	2.36 (2.18–2.56)†
Holman *et al*	Cohort Study	265 090‡	100% type 1 diabetes	$HbA_{1c} > 86$ mmol/mol (10%)	Mortality	2.19 (1.46–3.29)†
Holman *et al*	Cohort Study	2 889 210‡	100% type 2 diabetes	$HbA_{1c} > 86$ mmol/mol (10%)	Mortality	1.62 (1.48–1.79)†
Sardu *et al*	Retrospective	59	44%	Admission glycaemia > 7.7	Survival	0.285 (0.084–0.964)†
Li *et al*	Retrospective	269	19%	Hyperglycaemia	Mortality	1.77 (1.11–2.84)†
Zhu *et al*	Retrospective	818	100%	Median glycaemia during hospital stay 6.4 mmol/L (IQR 5.2–7.5)	Mortality	0.13 (0.04–0.44)†
Zhu *et al*	Retrospective	818	100%	Median glycaemia during hospital stay 6.4 mmol/L (IQR 5.2–7.5)	ARDS	0.41 (0.25–0.66)†
Zhu *et al*	Retrospective	818	100%	Median glycaemia during hospital stay 6.4 mmol/L (IQR 5.2–7.5)	Heart injury	0.21 (0.07–0.59)†
Zhu *et al*	Retrospective	818	100%	Median glycaemia during hospital stay 6.4 mmol/L (IQR 5.2–7.5)	Kidney injury	0.22 (0.05–1.03)†
Chen *et al*	Retrospective	904	15%	Hyperglycaemia	Mortality	1.08 (1.01–1.16)∫

ARDS: acute respiratory distress syndrome. *General practice records managed by The Phoenix partnership. † Adjusted hazard ratio. ‡Individuals registered with a general practice in England, UK. ∫ Adjusted odds ratio.

Figure 12. T2DM and COVID-19[2]

Key learnings

- Metformin does not need to be stopped in mild COVID-19 infection
- All oral antidiabetic agents should be stopped in diabetic patients admitted to ICU with severe COVID-19 infection.

References

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Disclaimer: *Dr Landi Lombard*
I received an honorarium for this talk and I serve on several advisory boards, including in the past for Merck.

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