

LETTER

Acute hyperglycaemic crisis after vaccination against COVID-19: A case series

Vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are the most important component of the global response to the COVID-19 pandemic. Although most adverse reactions observed have been mild, the emergence of more serious vaccine-associated adverse events is being closely monitored.

We observed three cases of acute hyperglycaemic crisis within 20–36 days of first administration of an adenovirus-vectored COVID-19 vaccine (ChAdOx1 nCoV-19) during a single week in April 2021. All patients were male, middle-aged, obese and dyslipidaemic, and two had pre-diabetes. Each presented with a subacute onset of osmotic symptoms without concurrent infection (including SARS-CoV-2) or a pre-existing diabetes diagnosis. Two patients required intensive care. Relatively low c-peptide measurements in the context of acute hyperglycaemia were observed, but with no other suggestion of autoimmunity. Extreme elevation of admission HbA_{1c} was seen across all cases, but we were unable to determine the time course during which the onset of hyperglycaemia had occurred (Table 1). Further clinical characteristics are detailed in Table 1.

Hyperglycaemic emergency presentations are relatively frequent in East London due to a high background prevalence of type 2 diabetes, including ketosis-prone subtypes. There were 72 hyperglycaemic emergency presentations to our hospital in the 6 months preceding these cases, of which only six were new diagnoses of diabetes: three of type 1 and three of type 2 diabetes. The cluster of three acute hyperglycaemic crises as first presentations of diabetes that we report here is therefore unusual.

Hyperglycaemia has been reported following COVID-19 vaccine administration, but the frequency is unclear. A single case of hyperglycaemic crisis following administration of a messenger RNA (mRNA)-based vaccine (BNT162b2) has been described in the United States.¹ In light of recent emergence of other Serious Adverse Events (SAEs), the possibility of a direct association between vaccination and acute hyperglycaemic crises should be considered.² All three patients described symptom onset within 1 week of vaccine administration and presented to hospital within 3–5 weeks.

Subacute presentation seems consistent with time course of other vaccine-associated SAEs (vaccine-induced thrombosis and thrombocytopenia [VITT] typically presents 4–28 days after vaccination with ChAdOx1 nCoV-19).

If causally associated with vaccination, such an effect could result from a generalised inflammatory response, or from a more specific reaction to vaccine constituents: impurities and/or excipients, the adenovirus vector or the SARS-CoV-2 spike protein immunogen encoded by the vector. ChAdOx1 nCoV-19 vaccine excipients are also not known to cause glycaemic changes. As our patients received vaccine doses from different batches, relation to impurities is unlikely.

Several adverse effects to other adenovirus-vectored vaccines have been previously described, including fasting hyperglycaemia.³ Adenovirus infection itself can also cause changes in insulin sensitivity.⁴ The vector component of some COVID-19 vaccines appears the most likely cause of SAEs given recent reports of VITT following administration of a second adenovirus-based agent.

In vaccine-associated adverse events, the phenomenon may not be specific to ChAdOx1 nCoV-19 or to adenovirus-vectored COVID-19 vaccines. Occurrence of our cases following administration of the ChAdOx1 nCoV-19 vaccine may simply reflect availability and administration of agents in the United Kingdom currently, and the common age of our patients the contemporary stage of progression of the UK vaccination programme. A more general immunogenic effect could also be considered, perhaps via induction of a glycaemic dysregulatory process like that seen in acute COVID-19, following SARS-CoV-2 spike antigen presentation. As the mode and pattern of antigen presentation is not vaccine-specific, we would then expect similar associations with mRNA vaccines.

Frequent uncontrolled hyperglycaemia has been reported in patients with COVID-19. Co-presentation of COVID-19 with acute hyperglycaemic crisis has been observed both in patients with and without pre-existing diabetes.⁵ Clinical and pathophysiological phenotypes are yet to be fully understood, but ketosis prevalence and unusually high insulin requirements seen are suggestive of severe insulin resistance

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and acute insulinopaenia, disproportionate to that occurring in the context of critical illness more generally.^{6,7}

Binding of angiotensin-converting enzyme 2 (ACE2) receptors, which are expressed in various metabolic tissues including pancreatic beta cells, has been implicated.⁸ SARS-CoV-2 replication within human beta cells has been demonstrated in vitro, and islet cell degeneration has been observed in COVID-19 patients post-mortem.^{9–11} There is an apparent association between acute-onset, ketosis-prone diabetes and ACE2 receptor binding for other coronaviruses.⁸ Increased renin–angiotensin system activation via ACE2 receptor downregulation following viral endocytosis may also impair insulin receptor signalling.¹² SARS-CoV-2-induced pro-inflammatory cytokine responses may contribute to both direct islet cell damage and impaired insulin receptor signalling. It is plausible that similar responses could follow SARS-CoV-2 antigen presentation after vaccination.

Finally, metabolic risk, although heterogeneous, is striking in these cases. All patients were male and either met criteria for or demonstrated several elements of metabolic syndrome prior to diabetes diagnosis. It may be that COVID-19 vaccination unmasks subclinical diabetes in predisposed individuals, and that our cases represent the most severe end of a spectrum of glucose dysregulation following COVID-19 vaccination. An interesting parallel can be drawn with susceptibility to COVID-19 itself, whether or not the effects and potential mechanisms are related.

We suggest that clinicians should enquire about recent COVID-19 vaccination in any patient presenting with acute hyperglycaemia and emphasise the importance of reporting potential associated cases to the appropriate regulatory authority. The overall benefits of COVID-19 vaccination outweigh the risk of adverse effects, particularly among those with greater metabolic risk. However, in case these presentations do reflect a causative association, it may be prudent to screen at-risk individuals for glycaemic dysregulation or advise more frequent patient self monitoring of capillary blood glucose following vaccination.

KEYWORDS

clinical diabetes, diabetes, in-patient diabetes, ketoacidosis, metabolic syndrome

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CONFLICT OF INTEREST

No conflicts of interest to disclose

What is already known?



- Most adverse reactions to COVID-19 vaccines have been mild; however more serious vaccine-associated adverse events are likely to emerge with advancing rollout.
- Hyperglycaemia has been reported following vaccine administration but the frequency is unclear and direct association has not yet been suggested.

What has been found?

- We describe three cases of acute hyperglycaemic crisis 3–5 weeks following first administration of an adenovirus-vectored COVID-19 vaccine presenting to a single hospital site within 1 week.

Clinical implications

- We discuss the possibility of an association between hyperglycaemic crisis and COVID-19 vaccination and suggest that clinicians should enquire about recent vaccine administration in any patient presenting with acute hyperglycaemia.

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TABLE 1 Clinical outcomes and demographic, anthropometric and admission biochemical characteristics of three patients presenting with acute hyperglycaemic crisis shortly following COVID-19 vaccination

	Case 1	Case 2	Case 3	Laboratory reference range
<i>Demographic and anthropometric parameters</i>				
Age	59	68	53	
Sex	Male	Male	Male	
BMI (kg/m ²)	31.12	32.51	35.05	
Ethnicity	Latino	White	Black	
<i>Medical background</i>				
Comorbidities	Hypertension, hypercholesterolaemia	Hypothyroidism, pre-diabetes	Hypertension, pre-diabetes	
Medications	Amlodipine, atorvastatin	Levothyroxine, omeprazole, colecalciferol	Amlodipine, indapamide	
Pre-episode HbA _{1c} (mmol/mol) (%)	38 (5.6%) (37 months prior)	47 (6.5%) (24 months prior)	44 (6.2%) (18 months prior)	
Vaccine first dose to presentation (days)	21	36	20	
<i>Biochemical parameters at admission</i>				
pH	7.383	7.218	7.385	7.35–7.45
Bicarbonate (mmol/L)	21.6	11.6	11.8	22.0–29.0
Lactate (mmol/L)	2.6	3.6	2.3	0.6–1.4
Capillary 3βhydroxybutyrate (mmol/L)	3.8	7.4	8.0	0–0.5
Serum osmolality (mosm/kg)	304.3	360.7	285.5	275–295
Glucose (mmol/L)	33	51	32	3.5–11
HbA _{1c} (mmol/mol) (%)	131 (14.1%)	137 (14.7%)	163 (17.1%)	<41 (<6%)
Sodium (mmol/L)	133	143	121	133–146
Potassium (mmol/L)	4.6	4.8	1.8	3.5–5.3
Urea (mmol/L)	5.3	23.7	9.5	2.5–7.8
Creatinine (μmol/L)	94	152	105	59–104
Triglycerides (mmol/L)	4.62	4.81	0.58	0–1.7
<i>Further investigation of diabetes</i>				
Diabetes triple antibody (GAD/IA2/ ZnT8) (unit/ml)	All negative	All negative	All negative	0–8
Serum c-peptide (pmol/L)	235	561	377	370–1470

(Continues)

TABLE 1 (Continued)

	Case 1	Case 2	Case 3	Laboratory reference range
Paired plasma glucose (mmol/L)	18.3	23.5	14.4	
CT pancreas	No evidence of malignancy		No evidence of malignancy	
<i>Clinical outcome</i>				
Diagnosis	Hyperglycaemic ketosis	Mixed HHS/DKA (HHS-predominant)	DKA	
Length of stay (days)	3	6	9	
Intensive care admission	No	Yes	Yes	

Cells are shaded where column headings are not applicable.

REFERENCES

1. Abu-Rumailah MA, Gharaibeh AM, Gharaibeh NE. COVID-19 vaccine and hyperosmolar hyperglycaemic state. *Cureus*. 2021;13(3):e14125.
2. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med*. 2021;384(22):2092–2101. <https://doi.org/10.1056/NEJMoa2104840>
3. Kremer EJ. Pros and cons of adenovirus-based SARS-CoV-2 vaccines. *Mol Ther*. 2021;28(11):P2303–P2304.
4. Jiang S, Gavrikova TA, Pereboev A, Messina JL. Adenovirus infection results in alterations of insulin signaling and glucose homeostasis. *Am J Physiol Endocrinol Metab*. 2010;298:E1295–E1304.
5. Huda M, Shaho S, Trivedi B, et al. Diabetic emergencies during the COVID-19 pandemic: a case-control study. *Diabet Med*. 2020;38(1):e14416.
6. Armeni E, Aziz U, Qamar S, et al. Protracted ketonaemia in hyperglycaemic emergencies in COVID-19: a retrospective case series. *Lancet Diabetes Endocrinol*. 2020;8(8):660–663.
7. Wu L, Girgis CM, Cheung NW. COVID-19 and diabetes: insulin requirements parallel illness severity in critically unwell patients. *Clin Endocrinol (Oxf)*. 2020;93(4):390–393. <https://doi.org/10.1111/cen.14288>
8. Yang J, Lin S, Ji X, Guo L. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol*. 2010;47:193–199.
9. Yang L, Han Y, Nilsson-Payant BE, et al. A human pluripotent stem cell-based platform to study SARS-CoV-2 tropism and model virus infection in human cells and organoids. *Cell Stem Cell*. 2020;27:125–136.
10. Müller JA, Groß R, Conzelmann C, et al. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. *Nature Metab*. 2021;3:149–165.
11. Yao XH, Li TY, Ping YF, et al. A pathological report of three COVID-19 cases by minimal invasive autopsies. *Chinese J Pathol*. 2020;49(5):411–417.
12. Sathish T, Tapp RJ, Cooper ME, Zimmet P. Potential metabolic and inflammatory pathways between COVID-19 and new-onset diabetes. *Diabetes Metabol*. 2021;47(2):101204.

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