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Covid-19, hypokalaemia and the renin-angiotensin-aldosterone system

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To the Editor

Biochemical disturbances are recognised in Covid-19 patients and have important implications in acute management and prognosis. Electrolyte disruptions, particularly hypokalaemia, predispose to the development of torsades de pointes and polymorphic ventricular tachycardia through QT interval prolongation. The risks are amplified by concomitant therapy with a variety of QT lengthening drugs used in the management of Covid-19 (such as hydroxychloroquine and macrolides) and by direct viral myocardial involvement. We read with interest the case study of persisting hypokalaemia by Alnafiey et al. [1] and their discussion of the multifactorial aetiologies of hypokalaemia in Covid-19. Our previously published experience in the United Kingdom may further unravel the multifaceted process of metabolic abnormalities within this context.

We observed hypernatraemia and hypokalaemia with normal renal function and variably new-onset hypertension among Covid-19 patients during the first wave of the pandemic. Two patients were investigated and found to have unexplained urinary potassium loss and hyporeninaemic hypoaldosteronism [plasma renin <0.2 nmol/L/hr (0.5–3.5) and aldosterone <60 pmol/L (60–250)]. Congenital forms of hypertension, glucocorticoid resistance, syndrome of apparent mineralocorticoid excess and hypothalamic-pituitary dysfunction were fully excluded in one and we treated this patient with amiloride. This apparently corrected serum/urinary electrolyte abnormalities and blood pressure within one week. Plasma renin and aldosterone were found normal after three weeks and amiloride was withdrawn. Thereafter the patient remained normotensive with a normal biochemical profile during recovery [2].

The diuretic amiloride inhibits sodium reabsorption by selectively blocking the sodium channel (ENaC) in the distal nephron [3,4] and hyporeninaemic hypoaldosteronism may be related to temporary dysregulated ENaC pathophysiology similar to that in Liddle's syndrome. Stabilisation of the renin-angiotensin-aldosterone system (RAAS) and distal tubulopathy (evident by reduction in renal potassium excretion) during convalescence supports a direct effect of SARS-CoV-2 on ENaC homeostasis. This is supported by the findings of Chen et al. [5]. The ongoing potassium loss described by Alnafiey et al. may signify prolonged RAAS disruption and tubulopathy resulting in a 'long Covid hypokalaemia' syndrome. It would be of interest if Alnafiey and colleagues were able to demonstrate and quantify ongoing renal wastage. It should be noted that hypomagnesaemia exacerbates hypokalaemia by increasing distal potassium secretion and renders it refractory to treatment; thus, each state may feed each other in a vicious circle.

The phenomenon (that we reported) may be adequately explained by downregulation of angiotensin converting enzyme 2 (ACE2) from viral binding resulting in upregulation of angiotensin 2 (ang 2) which enhances ENaC activity [6]. It has also been mentioned that accumulation of ang 2 may induce aldosterone secretion by the adrenal cortex leading to sodium reabsorption and potassium excretion from the collecting duct in kidney [7]. Although there is clearly a complex interplay between viral-ACE 2 binding and the RAAS with various ramifications, we suggest an "aldosterone-independent" process may be a principal underlying mechanism. Hyporeninaemic hypoaldosteronism reflects appropriate and intact RAAS homeostatic mechanisms in the face of hypertension and hypokalaemia.

Confounding factors, such as gastrointestinal losses, nutritional insufficiencies and drug-related renal potassium loss may muddy the waters leaving this metabolic profile overlooked in Covid-19 patients, and it must also be acknowledged that there could be considerable overlap in aetiologies of hypokalaemia. However, disruption of the RAAS may well be a critical factor and further studies on the effects of RAAS and viral ACE 2 binding should be undertaken to elucidate the underlying pathophysiologic mechanisms and potentially open up therapeutic avenues.

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Author contribution

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Consent

Written and signed consent was obtained from the patient discussed.

Registration of research studies

Not applicable.

Guarantor

AKJM and CGM accept full responsibility for the work.

Declaration of competing interest

No financial or personal conflicts of interest for any author.

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