Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Medical Hypotheses 144 (2020) 110220

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

COVID-19 and ethnicity: Does reduced responsiveness to glucocorticoids explain the more aggressive nature of disease among minorities?

Abhinav Karan[a], Kabeer Ali[a], Kirin Rambaran[b], Pedro Del Corral[c], Sateesh Sakhamuri[a,*], Surujpal Teelucksingh[a]

[a] Faculty of Medical Sciences, The University of the West Indies, St. Augustine, Trinidad and Tobago
[b] Thoracic Medical Department, Caura Hospital, Trinidad and Tobago
[c] Department of Physiology and Pathology, Burrell College of Osteopathic Medicine, Las Cruces, NM, USA

A B S T R A C T

Marked ethnic variations in complications and mortality have been noted following infection with COVID-19, with Black, Asian, and minority ethnic groups (BAME) being particularly hard hit. We hypothesise that glucocorticoid resistance stemming from several intrinsic reasons such as chronic social stress and lower circulating levels of Vitamin D may contribute to the exaggerated inflammatory response, more severe disease and poorer outcomes observed in BAME.

Background

Glucocorticoids are amongst the most effective anti-inflammatory agents in therapeutic use, exerting their effect by several synergistic mechanisms including reduction of oedema, cellular exudation, fibrin deposition, capillary dilatation and through inhibition of recruitment of neutrophils and monocytes. Clinicians commonly resort to them to treat a wide variety of disorders. In response to the unprecedented Coronavirus disease 2019 (COVID-19) pandemic, physicians have once again turned to this old friend as a potential treatment. COVID-19 can induce a life-threatening respiratory disorder, which is immunologically similar to sepsis-related adult respiratory distress syndrome (ARDS), that may require prolonged corticosteroid therapy [1]. The recent RECOVERY trial's preliminary report has shown the benefit of dexamethasone in severe COVID-19 disease, especially in patients requiring mechanical ventilation and oxygen supplementation [2]. Glucocorticoids are the only drugs that have produced survival benefit in the treatment of COVID-19 so far.

Nearly 700,000 people have succumbed to the COVID-19 pandemic thus far, but its toll has been particularly devastating among Black, Asian and minority ethnic (BAME) groups in the USA, UK, and Brazil. In the United States, the age-adjusted mortality rate among Blacks is 3.8 times, Hispanics 2.5 times, and Asians 1.5 times higher than Whites [3]. In the United Kingdom, the age-adjusted mortality rate among Blacks is 2.9 times, Pakistani and Bangladeshi 2.2 times, and South Indians 1.8 times than that of Whites [4]. Similarly, in Brazil, Black and Pardo (mixed) populations had the highest relative mortality rates for COVID-19. In fact, Pardo ethnicity was found to be the most significant risk factor apart from age for mortality [5]. Moreover, ethnic minorities were more likely to have been admitted to critical care and receive invasive mechanical ventilation than White patients, with South Asians in the UK being at higher risk of dying [4].

These marked ethnic disparities have been attributed to a greater burden of comorbidities in BAME; however, we believe that this explanation is premature and lacking. In this regard, CO-CIN data from Public Health England showed that of 30,693 patients with COVID-19, BAME patients were more likely to have diabetes, but less likely to have several other comorbidities such as chronic cardiac, pulmonary, renal, and neurologic disease [4]. In addition, multivariate analysis revealed that having diabetes only had a hazard ratio of 1.11 for mortality, when compared with chronic cardiac disease (1.20), chronic pulmonary disease (1.24), chronic kidney disease (1.28), and obesity (1.29) [6]. Furthermore, increasing age appears to be a significant determinant of poorer outcomes, yet only 30.7% of Black, 29.2% of Asians, and 35.2% of minority ethnicity patients hospitalized for COVID-19 were above the age of 70, as compared to 60.7% of Whites. Thus, young age is not a protective factor in BAME infected with COVID-19. If not comorbidities and age, what then? One should consider that the increased mortality seen in BAME may be a consequence of impaired glucocorticoid sensitivity stemming from several intrinsic reasons such as chronic social stress and lower circulating levels of Vitamin D.

* Corresponding author at: Department of Clinical Medical Sciences, Faculty of Medical Sciences, The University of the West Indies, Eric Williams Medical Sciences Complex, Trinidad, West Indies.
E-mail address: sateesh.sakhamuri@sta.uwi.edu (S. Sakhamuri).

https://doi.org/10.1016/j.mehy.2020.110220
Received 10 August 2020; Accepted 21 August 2020
Available online 27 August 2020
0306-9877/

Hypothesis

Firstly, we propose an ethnic variation in biological glucocorticoid sensitivity. Secondly, BAME groups are more likely to progress to severe disease and have poorer outcomes when infected with COVID-19 because of glucocorticoid resistance, which leads to an exaggerated inflammatory response. However, we acknowledge that BAME groups are more likely to become infected with COVID-19 for sociological reasons.

Support for the hypothesis

Cortisol and COVID-19 outcomes

Tissue corticosteroid resistance is a critical consequence of several acute and chronic inflammatory diseases, such as acute lung injury, systemic lupus erythematosus, and chronic obstructive pulmonary disease. COVID-19 has also been shown to induce a pro-inflammatory state, with elevations in numerous cytokines including interleukin-1 and tumour necrosis factor-alpha, both of which can reduce glucocorticoid receptor activity and induce glucocorticoid resistance [7]. Interestingly, as glucocorticoid therapy such as dexamethasone in the relatively low dose of 6 mg have been shown to improve survival in severe COVID-19 [2], if there are pre-existing conditions which may lead to down-regulation of the glucocorticoid receptor there will be a need for higher dosages to achieve the same therapeutic effect [8,9].

A recent report found that elevations in baseline random serum cortisol levels in patients with COVID-19 who presented to the hospital within 48 h of admission were predictors of poor prognosis [10]. A value greater than 744 nmol/L conferred a 42% increase in mortality after adjustment for age and other comorbidities. Cortisol was also shown to be a better indicator of mortality and reduced median survival than C-reactive protein, D-dimer, and neutrophil-to-leukocyte ratio. With higher serum cortisol predicting morbidity and mortality, the questions arise if more marked elevations of cortisol are simply reflecting the severity of the organism's stress response or revealing the presence of underlying glucocorticoid resistance?

BAME and variations of glucocorticoid resistance

The link between social status and chronic social stress and acquired glucocorticoid resistance has been extensively explored in primate and murine models, as well as humans with bronchial asthma [11]. Chronic psychosocial stress can lead to overactivity of the hypothalamic-pituitary axis, sympathetic adrenal medulla system, and pro-inflammatory immune response, resulting in a disturbed glucocorticoid balance counter-regulatory response that induces glucocorticoid resistance. There is evidence that clearly shows an inverse relationship between family income level and glucocorticoid resistance [12]. Chronic psychosocial stress in BAME is evident in the United States, where African-Americans are twice as likely to be unemployed, and minority groups are more likely to experience multi-dimensional poverty than white populations [12]. Thus, because of chronic social stress, BAME may be desensitized to the effects of circulating glucocorticoids and need to mount a higher than expected cortisol response when challenged by acute, severe illness. In other words, a higher cortisol response in BAME is likely a measure of impaired glucocorticoid sensitivity and, therefore, an inability to suppress inflammation triggered by infection with COVID-19.

Furthermore, the interplay of hypovitaminosis D on glucocorticoid sensitivity may add further relevance to the disparities seen in BAME. A recent study shows that a low plasma 25(OH)-Vitamin D level appears to be an independent risk factor for COVID-19 infection and hospitalization [13]. Vitamin D deficiency rates are higher among African Americans than Whites [14]. This is especially noteworthy given that Vitamin D sufficiency and its receptor activity have been shown to enhance the anti-inflammatory activity of glucocorticoid therapy [15]. By extension, its deficiency would lead to glucocorticoid resistance.

A measurement of glucocorticoid resistance in BAME

Previous work has shown that the skin vasoconstrictor response (SVC), a bioassay of topically applied glucocorticoids, is a measure of steroid potency and, more importantly, a measure of an individual's biologic responsiveness to glucocorticoids. Results from this bioassay have shown that whereas only about 10% of a Caucasian population will display some significant degree of SVC unresponsiveness, a very high proportion of Africans and South Asians failed to show any response, even to high potency agents like beclomethasone dipropionate in high concentrations. This is particularly so when associated with obesity and acanthosis nigricans, a marker of insulin and glucocorticoid resistance [9].

Evaluation of hypothesis

To assess the variation in glucocorticoid resistance across ethnicities, the skin vasoconstrictor assay, a long-established bioassay of glucocorticoid action, can be utilised in a cross-sectional study. This will require the recruitment of an adequate number of young, healthy volunteers of both genders and a broad cross-section of ethnicities, including Caucasians, First Nation Peoples/Native Americans, African, African Americans, Hispanics, Asians, and South Asians. Subjects should be excluded if they have elevated blood pressure or report a history of atherosclerotic cardiovascular disease, hypertension, diabetes mellitus, COPD, peripheral vascular diseases, cardiac/skeletal disease or any other disease requiring medical treatment, particularly intercurrent glucocorticoid therapy. Additionally, individuals with a history of prior allergic reactions to topical glucocorticoids should be excluded.

The skin vasoconstrictor (SVC) assay can be performed on the ventral forearm as previously described with appropriate test solutions containing a potent topical glucocorticoid like beclomethasone dipropionate dissolved in ethanol [8,9]. After evaporation, the forearm should be covered with an occlusive dressing for 16–17 h to be removed the following day. The degree of blanching can then be read by two trained observers blinded to the distribution of the test solution on the application sites. The following scale can be used: 0 (no blanching), 1 (faint pallor), 2 (moderate pallor), and 3 (intense pallor), 4 (intense pallor that spills beyond the margins). An absent or diminished blanching response will indicate absolute or relative glucocorticoid resistance.

Conclusion

Glucocorticoid resistance may contribute to the marked ethnic variation in morbidity and mortality observed in COVID-19. Ethnic variation in glucocorticoid sensitivity can be evaluated with the skin vasoconstrictor assay – a simple and cost-effective bioassay for testing this hypothesis.

Sources of support or funding

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Villar J, Confalonieri M, Pastores SM, Meduri GU. Rationale for prolonged corticosteroid treatment in the acute respiratory distress syndrome caused by

coronavirus disease 2019. Crit Care Explor 2020;2(4):e0111. Published 2020 Apr 29.
[2] RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report [published online ahead of print, 2020 Jul 17]. N Engl J Med. 2020;10.1056/NEJMoa2021436. doi:10.1056/NEJMoa2021436.
[3] Centers For Disease Control And Prevention. Coronavirus disease 2019 (COVID-19). (2020). URL: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/racial-ethnic-minorities.html.
[4] Harrison E. Ethnicity and outcomes from COVID-19 in UK hospital patients using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. (2020). URL: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/895695/S0452_CO-CIN_Ethnicity_and_Outcomes_from_COVID-19_in_UK_Hospital_Patients.pdf.
[5] Ribeiro H, Lima VM, Waldman EA. In the COVID-19 pandemic in Brazil, do brown lives matter? Lancet Glob Health 2020;8(8):e976–7.
[6] Ravi K. Ethnic disparities in COVID-19 mortality: are comorbidities to blame? Lancet 2020;396(10243):22.
[7] Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 Pneumonia in Wuhan, China [published online ahead of print, 2020 Mar 13]. JAMA Intern Med 2020;180(7):1–11.
[8] Brown PH, Teelucksingh S, Matusiewicz SP, Greening AP, Crompton GK, Edwards CR. Cutaneous vasoconstrictor response to glucocorticoids in asthma. Lancet 1991;337(8741):576–80.
[9] Teelucksingh S, Jaimungal S, Pinto Pereira L, Seemungal T, Nayak S. Does insulin resistance co-exist with glucocorticoid resistance in the metabolic syndrome? Studies comparing skin sensitivity to glucocorticoids in individuals with and without acanthosis nigricans. Cardiovasc Diabetol 2012;11:31.
[10] Tan T, Khoo B, Mills EG, et al. Association between high serum total cortisol concentrations and mortality from COVID-19. Lancet Diabetes Endocrinol 2020;8(8):659–60.
[11] Wright RJ. Stress and acquired glucocorticoid resistance: a relationship hanging in the balance. J Allergy Clin Immunol 2009;123(4):831–2.
[12] American Psychological Association, APA Working Group on Stress and Health Disparities. Stress and health disparities: Contexts, mechanisms, and interventions among racial/ethnic minority and low-socioeconomic status populations, (2017). URL: http://www.apa.org/pi/health-disparities/resources/stress-report.aspx (Accessed 13th July 2020).
[13] Merzon E, Tworowski D, Gorohovski A, et al. Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study [published online ahead of print, 2020 Jul 23]. FEBS J. 2020;10.1111/febs.15495. doi:10.1111/febs.15495.
[14] Nesby-O'Dell S, Scanlon KS, Cogswell ME, et al. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988–1994. Am J Clin Nutr 2002;76(1):187–92.
[15] Flayer CH, Larson ED, Haczku A. Breaking steroid resistance: effect of vitamin D on IL-23. Am J Respir Cell Mol Biol 2017;57(3):267–9.