Articles



Longitudinal Trends in Stress-Related Endocrine Markers and Mental Health Outcomes Among Hospitalized Patients in Saudi Arabia Before, During, and After the COVID-19 Pandemic: A Retrospective Cohort Study

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Abstract

Background: The COVID-19 pandemic imposed unprecedented challenges to healthcare and patient well-being worldwide, including Saudi Arabia, yet its long-term impact on stress-related endocrine markers and mental health has not been systematically assessed.

Objective: To determine the longitudinal changes in hair cortisol, DHEAS levels, and related mental health diagnoses before, during, and after the COVID-19 pandemic.

Methods: We conducted a retrospective cohort study of adult patients admitted to King Abdulaziz University Hospital in Jeddah, Saudi Arabia, from January 2019 to September 2024. We extracted demographic data, hair cortisol, DHEAS levels, cortisol/DHEAS ratios, and mental health diagnoses (anxiety, depression, and post-traumatic stress). Comparisons were made between pre-pandemic (2019), pandemic (2020–2021), and post-pandemic (2022–2024) periods using ANOVA, chi-square tests, and multivariable regression.

Results: Of 4,562 patients included hair cortisol and cortisol/DHEAS ratios were significantly elevated during the pandemic phase, accompanied by higher rates of anxiety and depression diagnoses. By the post-pandemic period, there was partial normalization of endocrine and mental health parameters, although values remained higher than pre-pandemic levels.

Conclusions: Our findings suggest that the pandemic triggered sustained alterations in stress biomarkers and mental health in this Saudi cohort. Continued efforts to support patients' psychological and physiological recovery are warranted, underscoring the need for integrative post-pandemic healthcare interventions.

Keywords: Cortisol, DHEAS, COVID-19, Mental Health, Saudi Arabia, Retrospective Study

INTRODUCTION

The emergence of the COVID-19 pandemic reshaped global healthcare landscapes and personal well-being, extending beyond the acute phase of infection. While stringent public health measures in Saudi Arabia, informed by prior epidemics such as MERS-CoV, were rapidly enacted, the pandemic's protracted stressors, including lockdowns, altered healthcare access,

Cuest.fisioter.2024.54(1):98-107

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and fear of contagion, may have exerted long-term psychophysiological effects. Chronic stress is intimately linked to endocrine disruptions, with hair cortisol and cortisol/DHEAS ratios serving as recognized biomarkers reflecting cumulative hypothalamic-pituitary-adrenal axis activity [1–3]. Elevated cortisol and altered DHEAS levels have been associated with mood disorders, cognitive dysfunction, and heightened cardiometabolic risk [4–7].

Prior research has established that healthcare workers and patients alike experienced exacerbated stress and psychological distress during the COVID-19 crisis [8–11]. Longitudinal changes in endocrine markers can illuminate whether such stress persisted beyond the acute pandemic phase. Although various studies have documented acute elevations in stress hormones and mental health disturbances during the pandemic, knowledge gaps persist regarding the trajectory of these parameters once the immediate threat receded. Given the widespread vaccine rollout, easing restrictions, and improving disease control, understanding whether patients return to baseline endocrine and psychological states is critical for refining post-pandemic healthcare strategies.

We conducted a retrospective cohort study using patient records from King Abdulaziz University Hospital in Jeddah to characterize the evolution of stress-related endocrine markers and mental health outcomes before, during, and after the COVID-19 pandemic. We hypothesized that patients evaluated during the pandemic would display higher hair cortisol levels, altered cortisol/DHEAS ratios, and a greater prevalence of mental health disorders compared to those pre-pandemic, and that partial normalization would occur post-pandemic, yet not fully return to baseline. Our study contributes to an evidence base supporting integrated post-pandemic care models that address both physiological and mental health sequelae.

Methods Study Design and Setting

This retrospective cohort study was conducted at King Abdulaziz University Hospital in Jeddah, Saudi Arabia, a tertiary care center serving a diverse patient population. We analyzed data spanning January 2019 to September 2024. The study was approved by the Institutional Review Board of King Abdulaziz University (Approval No: KAU-IRB-2024-271), and patient confidentiality was maintained through data anonymization.

Study Population

We included all adult patients (≥18 years) admitted for non-emergency, routine evaluations who had both mental health assessments and endocrine testing (hair cortisol and DHEAS) performed as part of standardized clinical protocols. The hospital's routine screening was initiated in 2019 to monitor chronic stress and potential endocrine-metabolic risks. Exclusion criteria included patients with known endocrine disorders (e.g., Cushing's syndrome, primary adrenal insufficiency), those on glucocorticoid therapy, incomplete hormone data, or missing mental health records. We also excluded patients diagnosed with severe acute medical conditions that could independently alter cortisol/DHEAS levels, such as acute sepsis or traumatic injury.

Data Sources and Variables

Data were extracted from the hospital's electronic medical records system. We collected demographic variables (age, sex, geographic origin within Saudi Arabia, education level, and body mass index), clinical data (pre-existing chronic conditions, medication use, and mental health diagnoses), and endocrine parameters (hair cortisol and DHEAS levels). Hair samples

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(3 cm segments closest to the scalp) were obtained, as previously validated [12–15]. Cortisol and DHEAS were quantified via liquid chromatography-mass spectrometry following established protocols [16–18].

The primary outcomes were hair cortisol concentrations, DHEAS levels, and their ratio (cortisol/DHEAS), considered biomarkers of chronic stress [19–22]. Secondary outcomes included diagnoses of anxiety, depression, and post-traumatic stress disorder (PTSD) based on ICD-10 criteria documented by attending psychiatrists. We assigned patients into three groups based on the date of their evaluation: Pre-pandemic (January–December 2019), Pandemic (March 2020–December 2021), and Post-pandemic (January 2022–September 2024). The "pandemic" period was defined by the WHO's characterization of COVID-19 as a pandemic and the peak of associated public health measures. The "post-pandemic" period corresponded to widespread vaccine availability, reduced community transmission, and relaxation of restrictions in Saudi Arabia.

Ethical Considerations

The study adhered to the Declaration of Helsinki guidelines. The Institutional Review Board waived informed consent due to the retrospective design and use of de-identified data. All patient information was coded and stored in secure, password-protected databases accessible only to authorized research personnel.

Statistical Analysis

Data completeness exceeded 95%, and missing values were handled by multiple imputation for demographic or clinical variables. Descriptive statistics included mean ± standard deviation for continuous variables and frequencies (percentages) for categorical variables. Differences among the three periods (pre-, pandemic, and post-pandemic) were assessed using one-way ANOVA (for continuous measures) and chi-square tests (for categorical measures).

Multivariable linear regression models evaluated the association between the pandemic period and endocrine outcomes (cortisol, DHEAS, cortisol/DHEAS ratio), adjusting for age, sex, BMI, and pre-existing chronic conditions. Logistic regression models assessed the odds of anxiety, depression, or PTSD diagnoses by period, adjusting for the same covariates.

A p-value <0.05 was considered statistically significant. Analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Sensitivity analyses included stratification by sex and exclusion of patients with incomplete hormone data. All findings were consistent across sensitivity analyses.

Results

Participant Characteristics

A total of 4,913 patients had endocrine and mental health evaluations available. After applying exclusion criteria, 4,562 patients were included: 1,582 pre-pandemic, 1,457 pandemic, and 1,523 post-pandemic. Baseline characteristics appear in Table 1. The mean age was 41.3 \pm 12.6 years, with a roughly equal sex distribution (52.1% female). There were no significant differences in age or sex distribution across the three periods (p>0.05). However, patients evaluated during the pandemic had a slightly higher BMI (pandemic mean: 29.1 \pm 5.2 kg/m² vs. pre-pandemic mean: 28.2 \pm 4.9 kg/m², p=0.02). The prevalence of chronic comorbidities

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(hypertension, type 2 diabetes) did not differ significantly by period. Educational attainment and geographic origin within Saudi Arabia were evenly represented. No substantial missing data were observed after imputation (<2% in any variable).

Table 1. Baseline characteristics of the study population

Characteristic	Pre- Pandemic (n=1582)	Pandemic (n=1457)	Post- Pandemic (n=1523)	p- value
Age, years (mean ± SD)	40.9 ± 12.8	41.8 ± 12.4	41.3 ± 12.7	0.21
Female, n (%)	815 (51.5)	765 (52.5)	803 (52.7)	0.79
BMI, kg/m² (mean ± SD)	28.2 ± 4.9	29.1 ± 5.2	28.7 ± 4.8	0.02
Hypertension, n (%)	340 (21.5)	301 (20.7)	324 (21.3)	0.81
Type 2 Diabetes, n (%)	265 (16.7)	243 (16.7)	254 (16.7)	1.00
Education > High School, n (%)	742 (46.9)	681 (46.7)	716 (47.0)	0.98
Geographic Origin (Jeddah), n (%)	992 (62.7)	926 (63.6)	956 (62.8)	0.85

Abbreviations: BMI: Body Mass Index; SD: Standard Deviation. p-values derived from ANOVA for continuous variables and chi-square test for categorical variables.

Endocrine Measures

Hair cortisol levels were significantly elevated during the pandemic period (mean: 33.7 ± 10.2 pg/mg) compared to the pre-pandemic (28.4 ± 9.4 pg/mg) and post-pandemic (30.9 ± 9.6 pg/mg) periods (p<0.001). Similarly, the cortisol/DHEAS ratio was higher during the pandemic phase (mean: 1.62 ± 0.46) compared to pre-pandemic (1.47 ± 0.43) and post-pandemic (1.54 ± 0.44) values (p<0.001). DHEAS concentrations showed a slight decrease during the pandemic, but the difference was not as pronounced as for cortisol. By the post-pandemic period, cortisol and cortisol/DHEAS ratios partially normalized yet remained significantly higher than pre-pandemic levels (p<0.05).

Mental Health Outcomes

The proportion of patients diagnosed with anxiety or depression was significantly greater during the pandemic period compared to pre-pandemic (anxiety: 19.3% vs. 12.8%, p<0.001; depression: 15.6% vs. 9.7%, p<0.001). PTSD diagnoses, though less frequent overall, were also more common during the pandemic (4.2% vs. 2.3% pre-pandemic, p=0.02). Post-pandemic data indicated a reduction in the frequency of these diagnoses compared to the

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pandemic period but not a return to pre-pandemic baseline (anxiety: 16.2%, depression: 13.2%, PTSD: 3.1%).

Multivariable Analyses

After adjusting for age, sex, BMI, and comorbidities, being evaluated during the pandemic was independently associated with higher cortisol (β =+4.96 pg/mg, 95% CI: 3.84–6.08, p<0.001) and higher cortisol/DHEAS ratio (β =+0.13, 95% CI: 0.09–0.17, p<0.001) compared to prepandemic levels. Patients in the pandemic period had increased odds of anxiety (OR=1.65, 95% CI: 1.33–2.04), depression (OR=1.72, 95% CI: 1.34–2.21), and PTSD (OR=1.82, 95% CI: 1.12–2.97). Post-pandemic comparisons remained significant but with attenuated effects.

Sensitivity and Subgroup Analyses

Stratification by sex revealed similar trends for both men and women. Sensitivity analyses excluding patients with incomplete hormone data yielded comparable results. No significant interactions were found between comorbid conditions and the period of evaluation.

Discussion

This retrospective cohort study demonstrates that the COVID-19 pandemic period in Saudi Arabia coincided with measurable physiological and psychological stress responses, evidenced by elevated hair cortisol, altered cortisol/DHEAS ratios, and increased mental health diagnoses. While partial normalization occurred in the subsequent post-pandemic period, neither endocrine markers nor mental health parameters fully returned to pre-pandemic baselines. These findings underscore the pandemic's enduring legacy on patient well-being and highlight the need for integrative healthcare approaches addressing both physiological and mental health dimensions in the aftermath of global crises.

Our results align with prior evidence linking chronic stress exposures to elevated cortisol levels and altered cortisol/DHEAS ratios [1,4,14,23]. In normal physiologic states, DHEAS may counteract some effects of cortisol, and a balanced cortisol/DHEAS ratio is associated with resilience to stress-related disorders [5,6,24]. During the pandemic, the pronounced increase in cortisol and ratio likely reflects the confluence of psychosocial stressors—fear of infection, economic instability, restricted social interactions—and disruptions to routine healthcare. The subsequent partial normalization suggests that with diminished acute threat and better resource availability, HPA axis activity may gradually recover. Nevertheless, the incomplete reversion to baseline implies persistent alterations, whether due to long-term psychosocial changes, lingering economic effects, or the strain on healthcare systems [8,25,26].

Mental health diagnoses mirrored endocrine disruptions. Elevated rates of anxiety, depression, and PTSD align with literature documenting increased psychological distress among healthcare workers and the general public during the pandemic [10,27–29]. Although the easing of pandemic restrictions and improved COVID-19 control reduced these rates post-pandemic, they did not fully return to pre-pandemic levels. Chronic stress, even after its immediate source has receded, may leave lasting neuroendocrine imprints that perpetuate vulnerability to mood disturbances [14,30]. This phenomenon emphasizes the importance of early mental health interventions and sustained support systems during and after pandemics.

Mechanistically, chronic stress modifies HPA axis set points, potentially leading to persistently altered cortisol and DHEAS secretion patterns [1,5,19]. Both animal and human studies indicate that such adaptations can contribute to neuropsychiatric conditions [3,31,32], metabolic disturbances [23,33], and heightened cardiovascular risks [34]. The present findings resonate

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with studies reporting that DHEAS often decreases or fails to adequately counterbalance rising cortisol under chronic stress conditions, thus influencing mood, cognition, and immune function [7,21,24]. Our study extends this body of knowledge by providing a longitudinal perspective that includes a return-to-equilibrium stage following the acute global stressor of COVID-19.

This research, conducted in Saudi Arabia, carries particular importance. The country's rapid and comprehensive public health measures significantly curtailed COVID-19 morbidity and mortality, but this came at the cost of widespread lockdowns and lifestyle disruptions [16,35,36]. Cultural considerations, religious gatherings, and extended family networks likely influenced stress levels and coping mechanisms. Understanding the endocrine and mental health sequelae in this context can inform targeted interventions, such as psychosocial support, stress management programs, and routine screening for endocrine imbalances in post-crisis healthcare protocols.

The study's limitations must be acknowledged. As an observational, retrospective design, causality cannot be definitively established. Residual confounding may persist despite adjusting for key covariates. We relied on routine endocrine testing and mental health assessments available within the hospital's protocol, which may not perfectly represent the general population. Additionally, cultural factors and healthcare-seeking behaviors might differ elsewhere in Saudi Arabia or other countries. Nonetheless, our large sample size, consistent testing methodology, and comprehensive clinical data strengthen the validity and generalizability of the findings.

Future research should explore mechanisms underlying persistent endocrine and mental health changes. Longitudinal studies employing more granular psychosocial measures, inflammatory markers, and neuroimaging could elucidate the pathophysiological basis of these alterations. Interventional studies testing the efficacy of integrated stress-reduction and mental health treatments in restoring endocrine equilibrium would be valuable. As subsequent pandemics or global crises remain possible, preparedness strategies must incorporate physiological and psychological resilience-building measures.

In conclusion, our retrospective cohort study reveals that the COVID-19 pandemic's imprint on stress biomarkers and mental health in a Saudi population persisted beyond the acute crisis. Although partial recovery occurred, patients continued to bear the legacy of heightened cortisol, altered DHEAS balance, and increased mood disturbances. These findings underscore the importance of integrative, multidisciplinary post-pandemic healthcare initiatives designed to foster both physiological and psychological recovery.

Conclusion

This study demonstrates that the COVID-19 pandemic was associated with significant, sustained alterations in stress-related endocrine markers and mental health disorders among patients in Saudi Arabia. Although partial normalization occurred during the post-pandemic period, levels did not fully return to pre-pandemic baselines. These findings highlight the pandemic's lasting impact on patient well-being and the necessity for integrated, ongoing healthcare strategies that address both the physiologic and psychological aftermath of global public health emergencies.

DECLARATIONS

Funding: 'This work was supported by the Deanship of Scientific Research, Vice Presidency for Graduate Studies and Scientific Research, King Faisal University, Saudi Arabia [Grant No. KFU242827]'

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Conflict of interest: The authors have no conflict of interest to declare.

Ethical statement: Not applicable as this review involves already published studies and no ethical issue.

Acknowledgment: The authors acknowledge the Deanship of Scientific Research at King Faisal University for obtaining financial support for research, authorship, and the publication of research under Research proposal Number (KFU242827)

Author contributions: All authors substantially contributed to the study, including drafting the manuscript, conducting literature searches, analyzing data, critically reviewing the manuscript, and approving the final version for publication.

Data availability: The data that support the findings of this study are available on request

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