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Literature Study: Cortisol Hormone to DHEA-S Ratio as an Indicator of HPA Axis Activity in Chronic Stress and Insulin Resistance

Odor Debora Pita Uli Sinaga[1] Febry Yeni Gultom[2] Judika Adventist Maleakhi Sihite[3] Naomi Putri Chelsea Solin[4] Melva Silitonga[5]
Departmen of Biology, Faculty of Mathematics and Science, Universitas Negeri Medan, Deli Serdang, North Sumatera, Indonesia[1,2,3,4,5]
Email: odordeborapitaulisinaga@gmail.com[1] febryyenigultom@gmail.com[2] judikasihite03@gmail.com[3] naomisolin22@gmail.com[4] melvasilitonga@unimed.ac.id[5]

Abstrak

Stres kronis dapat mengganggu regulasi aksis Hipotalamus-Pituitari-Adrenal (HPA), menyebabkan disregulasi sekresi kortisol dan ketidakseimbangan rasio kortisol terhadap dehidroepiandrosteron sulfat (DHEA-S), yang berimplikasi pada perkembangan resistensi insulin dan Diabetes Melitus Tipe 2 (DMT2). Kortisol, sebagai antagonis insulin, meningkatkan produksi glukosa hepatik dan mengurangi pengambilan glukosa perifer, sedangkan DHEA-S memiliki efek protektif terhadap metabolisme glukosa. Studi literatur ini bertujuan untuk mengevaluasi bukti-bukti terkait peran rasio kortisol/DHEA-S sebagai biomarker potensial dalam hubungan antara stres kronis dan resistensi insulin. Metode yang digunakan adalah sintesis kritis terhadap penelitian terdahulu mengenai mekanisme aksis HPA, dampak stres terhadap metabolisme glukosa, serta signifikansi klinis rasio kortisol/DHEA-S. Hasil analisis menunjukkan bahwa ketidakseimbangan rasio kortisol/DHEA-S akibat stres kronis berkontribusi pada gangguan sensitivitas insulin, memperkuat pentingnya pendekatan biomarker ini dalam manajemen risiko DMT2. Studi ini menyoroti perlunya penelitian lebih lanjut untuk memvalidasi penggunaan rasio kortisol/DHEA-S sebagai alat prediktif dan intervensi terapeutik.

Kata Kunci: *Stres kronis, aksis HPA DHEA-S, resistensi insulin, Diabetes Melitus Tipe 2*

Abstract

Chronic stress can disrupt the regulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis, causing dysregulation of cortisol secretion and an imbalance in the ratio of cortisol to dehydroepiandrosterone sulfate (DHEA-S), which is implicated in the development of insulin resistance and Type 2 Diabetes Mellitus (T2DM). Cortisol, as an insulin antagonist, increases hepatic glucose production and reduces peripheral glucose uptake, while DHEA-S has a protective effect on glucose metabolism. This literature review aims to evaluate the evidence related to the role of the cortisol/DHEA-S ratio as a potential biomarker in the relationship between chronic stress and insulin resistance. The method used is a critical synthesis of previous studies on the mechanism of the HPA axis, the impact of stress on glucose metabolism, and the clinical significance of the cortisol/DHEA-S ratio. The results of the analysis indicate that an imbalance in the cortisol/DHEA-S ratio due to chronic stress contributes to impaired insulin sensitivity, reinforcing the importance of this biomarker approach in the management of T2DM risk. This study highlights the need for further research to validate the use of the cortisol/DHEA-S ratio as a predictive tool and therapeutic intervention.

Keywords: Chronic stress, HPA axis DHEA-S, Insulin resistance, Type 2 Diabetes Mellitus

INTRODUCTION

Stress is a multifaceted adaptive response to homeostatic challenges, which is primarily regulated through the hypothalamic-pituitary-adrenal (HPA) axis. Activation of this neuroendocrine pathway triggers the release of glucocorticoids, such as cortisol in humans, which regulate important physiological processes including glucose metabolism, immune modulation and inflammatory responses (Ahmad et al., 2023; McEwen, 2007; Joseph & Golden,

2017). While the acute stress response is evolutionarily beneficial, allowing organisms to cope with immediate threats and restore balance, chronic or repeated exposure to stress can lead to dysregulation of the HPA axis. This maladaptive state is characterized by altered cortisol secretion patterns, reduced glucocorticoid receptor sensitivity, and impaired negative feedback mechanisms (Joseph & Golden, 2017; Johnson et al., 2019), which leaves individuals vulnerable to a spectrum of metabolic disorders. Prolonged HPA axis activation and sustained elevation of cortisol have been linked to the pathogenesis of insulin resistance and type 2 diabetes mellitus (T2DM). Cortisol counteracts the action of insulin by promoting hepatic gluconeogenesis and inhibiting peripheral glucose uptake in target tissues (Joseph & Golden, 2017).

Furthermore, chronic stress may exacerbate T2DM risk factors, including obesity and sedentary behavior, through behavioral and metabolic pathways (Gianotti et al., 2021; Fitri et al., 2021). However, emerging evidence highlights the potential role of dehydroepiandrosterone sulfate (DHEA-S), an abundant adrenal steroid with insulin-sensitivity-enhancing and immunomodulatory properties, as a counterweight to the metabolic effects of cortisol (Endocrine, 2021). Consequently, the cortisol to DHEA-S ratio has gained attention as a biomarker reflecting HPA axis activity and its systemic health implications, which offers a more nuanced perspective than isolated cortisol measurements. Despite progress in understanding the interplay between chronic stress, HPA axis dysfunction, and insulin resistance (Joseph & Golden, 2017; Nuralita et al., 2023), the clinical relevance of the cortisol to DHEA-S ratio remains unexplored. This review critically synthesizes existing evidence to elucidate the relationship between chronic stress, HPA axis activity (as measured by this ratio), and insulin resistance. By evaluating mechanistic and clinical studies, we aim to clarify the utility of biomarkers in metabolic health surveillance and identify gaps for future research, ultimately informing targeted interventions for stress-related metabolic disorders.

RESEARCH METHODS

The research method used is Qualitative Research with types of research including: Literature Collection. Literature collection was conducted through searches in various reputable scientific databases, including PubMed, Google Scholar, ScienceDirect, Scopus, and ProQuest, as well as specialized journals in the field of endocrinology and metabolism. The search used keywords related to chronic stress, HPA axis, cortisol, DHEA-S, insulin resistance, and type 2 diabetes mellitus to ensure relevance of the topic.

Inclusion Criteria

The inclusion criteria applied included: (1) original research articles in the form of experimental, clinical, or observational studies, (2) systematic reviews and meta-analyses, (3) publications in the last 10-15 years (except essential references), (4) focus on the relationship of chronic stress with HPA axis dysregulation and insulin resistance, and (5) available in English or Indonesian with full text.

Exclusion Criteria

Ineligible studies were excluded based on: (1) availability of only abstracts without full text, (2) weak research methodology, (3) focus on acute stress without metabolic linkage, (4) animal studies without clinical relevance, and (5) opinion or narrative articles without empirical data support.

Selection Process

The selection process was conducted in stages including: (1) initial screening based on title and abstract, (2) full text evaluation, (3) critical analysis of methodological quality, and (4)

synthesis of findings based on related themes. Reference management utilized Zotero/Mendeley to ensure citation accuracy and avoid duplication.

Selection Results

From more than 15 articles identified, 10 studies were selected that met the criteria. These studies covered various aspects including biological mechanisms, clinical evidence and interventions regarding the role of cortisol/DHEA-S ratio in chronic stress and metabolic disorders. This systematic approach enabled a comprehensive analysis of the potential of the cortisol/DHEA-S ratio as a biomarker of chronic stress and its implications for insulin resistance.

RESEARCH RESULTS AND DISCUSSION

Chronic stress has long been associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which plays an important role in the pathogenesis of various metabolic disorders, including insulin resistance and type 2 diabetes mellitus (T2DM). One of the key indicators to assess HPA axis activity is the cortisol to dehydroepiandrosterone sulfate (DHEA-S) ratio. Cortisol, as the main glucocorticoid hormone, functions to increase energy availability through gluconeogenesis and lipolysis. However, chronic exposure to high cortisol levels may induce insulin resistance and visceral fat accumulation. On the other hand, DHEA-S, produced by the reticular zone of the adrenal gland, has antagonistic effects to cortisol through its anti-inflammatory and neuroprotective properties. Thus, the cortisol/DHEA-S ratio reflects the balance between the catabolic effects of cortisol and the anabolic effects of DHEA-S, which is particularly relevant in the context of adaptation to chronic stress.

Discussion

Cortisol as a Biomarker of Chronic Stress

The study by Noushad et al. (2021) highlighted that cortisol is a major biomarker of chronic stress that can be measured through various biological media, such as hair, saliva and urine. Persistent elevated cortisol levels are associated with hyperactivation of the HPA axis, which has the potential to trigger metabolic disorders, including obesity and diabetes. This finding is in line with Haryono & Handayani's (2021) research, which reported that stress in T2DM patients correlates with excess cortisol production, which further reduces insulin sensitivity and increases blood glucose levels. This is reinforced by the research of Fitri et al. (2021), who found a significant relationship between stress levels and elevated blood sugar levels in overnourished police, where stress triggers excessive cortisol production that interferes with glucose metabolism.

HPA Axis Dysfunction and Insulin Resistance

Joseph and Golden (2017) indicated that HPA axis dysfunction, including flattening of the diurnal cortisol curve, is associated with insulin resistance and T2DM. Individuals with diabetes tend to show a higher cortisol/DHEA-S ratio, reflecting the predominance of cortisol's catabolic effects. The study by Yuliadi (2021) sheds light on the neuroendocrine mechanisms behind the link between stress and psychosomatic disorders, including how excessive activation of the HPA axis can lead to decreased immunity and metabolic disorders. In addition, research by Azzahra et al. (2025) emphasized the importance of the dynamic interaction between cortisol and DHEA-S in metabolic regulation. DHEA-S is known to mitigate the negative effects of cortisol through increased insulin sensitivity and tissue protection against oxidative damage. However, under chronic stress, DHEA-S production often decreases, thus exacerbating the imbalance in the cortisol/DHEA-S ratio.

Mathematical Model of the HPA Axis

Mathematical studies of the HPA axis provide additional insights into the dynamics of cortisol and the stress response. These models integrate factors such as hippocampal receptors on CRH secretion, the role of Arginine Vasopressin (AVP) in ACTH production, and circadian rhythms. The models also highlight the complexity of negative feedback in the HPA axis, which can be disrupted under conditions of chronic stress, exacerbating metabolic dysregulation.

CONCLUSION

Based on a review of the literature, chronic stress causes HPA axis dysregulation, characterized by an increase in the cortisol/DHEA-S ratio. This imbalance plays an important role in the pathogenesis of insulin resistance and T2DM through the mechanisms of increased gluconeogenesis, decreased insulin sensitivity, and visceral fat accumulation. These findings underscore the importance of therapeutic interventions targeting cortisol/DHEA-S balance, such as stress management therapy, lifestyle modification, or DHEA-S supplementation, to prevent or address the impact of chronic stress on metabolic health. Further studies are needed to explore the potential of specific and effective therapies in normalizing the cortisol/DHEA-S ratio in at-risk populations.

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