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Association Between Stress Hormones and Menopausal Symptoms in Iraqi Postmenopausal Women

Nibras Abbas AL-Mansouri
Department of Pathological Analysis, College of Science, Al-Qasim Green University, Al-Qasim 51013, Iraq

Abstract

There is increasing evidence that dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis may play a role in the etiology and severity of symptoms of menopause but the data are scarce regarding stress hormones in postmenopausal women with limited data from Middle Eastern population. The aim of this study was to examine serum levels of cortisol, ACTH, and DHEA and their associations with menopausal symptoms in postmenopausal women in Iraq. We used a cross-sectional comparative design including 68 postmenopausal women and 42 age-matched premenopausal controls. The information regarding menopausal symptoms was obtained via structured questionnaires, meanwhile, serum cortisol, ACTH, and DHEA concentrations were measured by enzyme-linked immuno-sorbent assay (ELISA). Cortisol in postmenopausal women had significantly higher concentrations of cortisol (18.6 ± 4.2 µg/dL vs. 13.9 ± 3.6 µg/dL, $P < 0.02$) and ACTH (46.3 ± 10.8 pg/mL vs. 38.1 ± 9.4 pg/mL, $P < 0.03$), along with significantly lower concentrations of DHEA (88.21 ± 12.3 µg/dL vs. 95.4 ± 18.9 µg/dL, $P < 0.017$), compared with premenopausal women. Postmenopausal participants experienced significantly higher prevalence of menopausal symptoms, especially hot flashes (78.0%), sleep disturbances (69.1%), and mood disturbances (64.7%). Hot flashes (P=0.02; P=0.01), sleep disturbance (P=0.03; P=0.04), and mood disturbances (P=0.04; P=0.02) were significantly associated with elevated cortisol and ACTH levels, respectively. By contrast, lower DHEA was independently associated with lack of libido ($P = 0.001$) and vaginal dryness ($P = 0.03$). Such stress hormone imbalance is associated with menopausal symptomatology, which suggests that stress-related hormonal assessment should be included to the bedside evaluation of postmenopausal women.

Keywords: Cortisol, ACTH, DHEA, Premenopausal, Postmenopausal

Introduction

Menopause is a very important stage in the life of any woman which causes permanent cessation of menstruation and reduction in ovarian hormone production. For postmenopausal women, decreasing levels of estrogen and less critically, progesterone and other sex steroids are related to numerous somatic, psychological and vasomotor symptoms such as hot flushes, night sweats, mood problems accompanied by sleep disorders and cognitive complaints (Kaya et al., 2017). These symptoms, together characterized as the menopause symptom spectrum, are associated with reduced quality of life and higher healthcare utilization in this population. It is now becoming accepted that endocrine alterations due to and after menopause are not limited to reproductive ones, but also involve the HPA axis and other stress-related hormonal systems (Motlani et al., 2023).

Of all stress hormones, cortisol is the key biomarker of HPA axis activity, and this system has a central role in controlling metabolic, immune and psychological responses to stress. Previous studies are consistent with the finding that cortisol elevations may occur during the MT and early postmenopause, reflecting alterations in stress hormone production following reproductive hormone decline (Woods et al., 2009). Morever, higher urinary and salivary cortisol has been associated with greater severity of vasomotor and mood symptoms. These results suggest that stress hormones may not only serve as physiological responses to stress, but also relate with menopausal symptoms and possibly affect overall health outcomes. Such relationships are important as high cortisol levels are associated with negative health outcomes such as disruption in sleep, mood disorders and metabolic shifts, which may additionally augment menopause-related symptoms (Woods et al., 2006 ; Cay et al., 2018).

Postmenopausal women from Middle Eastern countries, including Iraq, are still the subject of little data with respect to stress hormone dynamics, which play an evident role in menopause. Most of the available evidence comes from studies in Western population, which social environmental and lifestyle are quite different comparing both to Iraq. For instance, socioeconomic factors, dietary habits and psychosocial stressors specific to Iraqi women could modulate expression of menopausal symptoms and hormonal stress responses. Research of psychological symptoms such as depression and anxiety in iraqi's menopausal women are also demonstrating strong prevalence rates It is therefore important to investigate the biological counterparts of these complaints, e.g. cortisol and other stress hormones (Abdulkarim et al., 2024).

In synergy with HPA-axis hormones, such as adrenalin and noradrenaline, beside cortisol, may mediate an interaction between state of reproductive hormones changes – leading to varied profiles of symptoms. Estrogen decline-induced interplay between hormones can influence neurotransmitter systems as well as stress hormone receptors and consequently could affect mood, cognition, and global stress responses (Hantsoo et al., 2023). Such interactions may increase the risk of stress-related symptoms, especially in women who have preexisting psychosocial stressors/other kinds of comorbidities. Disrupted stress hormones have also been investigated in menopausal insomnia, with abnormalities in autonomic and cortisol reactivity to stress noted, providing further evidence for the contribution of stress hormones to symptomatology independent of reproductive hormones (Yuksel et al., 2021).

For the individual health effect, stress hormone changes in PMW have more public health implications. Cortisol and stress hormone levels may be elevated, leading to longer term risks for increased cardiovascular disease, osteoporosis, and metabolic syndrome. Such conditions are common among older women, have been associated with menopausal status and chronic stress exposure. Management of stress hormone regulation therefore may have potential to serve a dual purpose in alleviating symptoms and halting progression to chronic diseases. It is with comprehensive studies that hormonal biomarkers are guide behavior/e and to explore better (such as through the symptom profiles) in these complex relationship (Sic et al., 2024).

The current study was carried out to analyse the association of some important stress-related hormones, cortisol, adrenocorticotropic hormone (ACTH), and dehydroepiandrosterone (DHEA) with the severity of menopausal symptoms in postmenopausal women living in Iraq. The purpose of this research is to elucidate the contribution of hypothalamic–pituitary–adrenal axis activity to menopausal symptom expression by exploring associations between these hormonal biomarkers and physical, psychological and vasomotor symptom domains.

Methods

Patients and data collection

Al-Zahra Teaching Hospital, Al-Najaf City, Iraq; Cross-sectional observation study done over a period of 6 months (July-

2025 through January-2026). The objective of the study was to assess the relationship between stress-associated hormonal profiles and menopausal symptoms in postmenopausal women.

Study Population

A total of 68 postmenopausal women participated in the study, in addition to 42 premenopausal women as a control. Postmenopausal was defined as no menstruation for not less than 12 months. Patients were recruited from the gynecology, and internal medicine outpatient clinics of Al-Zahra University Hospital. Women were eligible if they reported any one or more menopausal symptoms: hot flashes, night sweats, vaginal dryness, sleep disturbance, mood swings and decrease in libido. Those who had a history of chronic systemic diseases including diabetes mellitus, cardiovascular disease, autoimmune diseases, malignancies, chronic inflammatory disorders and diagnosed psychiatric diseases were excluded. To limit endocrine confounding, women with known primary endocrine disease (e.g., thyroid, adrenal, pituitary or gonadal diseases), using hormone replacement therapy, systemic corticosteroids or other drugs affecting the HPA axis within 3 months before inclusion were also excluded.

Data Collection

Demographic and clinical characteristics were obtained through a structured questionnaire with variables such as age, marital status, body mass index (BMI), years of menopause; in addition, detail evaluation of climacteric symptomatology. The severity of symptoms were written down on subjective frequencies and intensities. BMI was the weight in kilograms (kg) divided by height squared in meters (m^2), and according to World Health Organization (WHO) standards, it was categorised as follows: underweight (<18.5), normal weight (18.5–24.9), overweight (25–29.9) and obese (≥30).

Blood samples collection and hormonal assays

Fasting morning venous blood samples were drawn for all patients between 8:00 a.m. and 9:30 a.m. in order to adjust to circadian fluctuations in the release of stress hormones. Under a sterile condition, blood samples were obtained and clotted at room temperature, followed by centrifugation at 3,000 rpm for 10 min. Immediately after collection, serum was centrifuged and the supernatant frozen at –20°C for future analysis. The serum levels of cortisol, adrenocorticotropic hormone (ACTH) and dehydroepiandrosterone (DHEA) were determined using ELISA kits as per the manufacturer`s instructions. In brief, the serum was applied into microplate wells coated with specific hormone antibodies and then incubated with biotinylated detection antibodies and streptavidin conjugate of horseradish peroxidase. The color intensity was developed by TMB substrate and read at a wavelength of 450 nm with a microplate reader. Calibration curves were established for the hormones. All samples were run in duplicate with intra- and inter-assay coefficients of variation remaining less than 10%.

Ethical Considerations

The research protocol was approved by the Ethics Committee of Al-Zahra Teaching Hospital. All study participants gave their written and informed consent before being included in the study. Ethical Compliance The study was performed in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

The statistical package for the social sciences IBPSS) 25 version program (SPSS, Inc., Chicago, IL) was used for data analyses. Kolmogorov–Smirnov test was used to check normality of continuous variables. Results are given as mean ± standard deviation (SD) for normally-distributed variables and median and interquartile range (IQR) for non-normally distributed data. Station correlations between serum hormone levels and menopausal symptom severity were applied, the Pearson's or Spearman's correlation coefficient if appropriate. A $p < 0.05$ was considered as statistically significant.

The Results

Prevalence of obesity Fig 2 shows the distinct distribution of BMI between premenopausal and postmenopausal women. Overall, 36% of the premenopausal women were within the normal BMI range, followed by overweight (28%) and a lower percentage in obese category (16%) or underweight category (18%). In postmenopausal women, there was a more overt shift towards the higher BMI categories with a larger proportion being obese (39%) or overweight (33%), and 20% of normal weight but only 8% were underweight. In general, the pattern of the figure is that body weight goes up as menopausal status increases and that menopause may be related to at least undesirable changes in body composition. Such a change might have an impact on metabolic health, adrenal hormone release and postmenopausal symptomatology in the central menopause period.

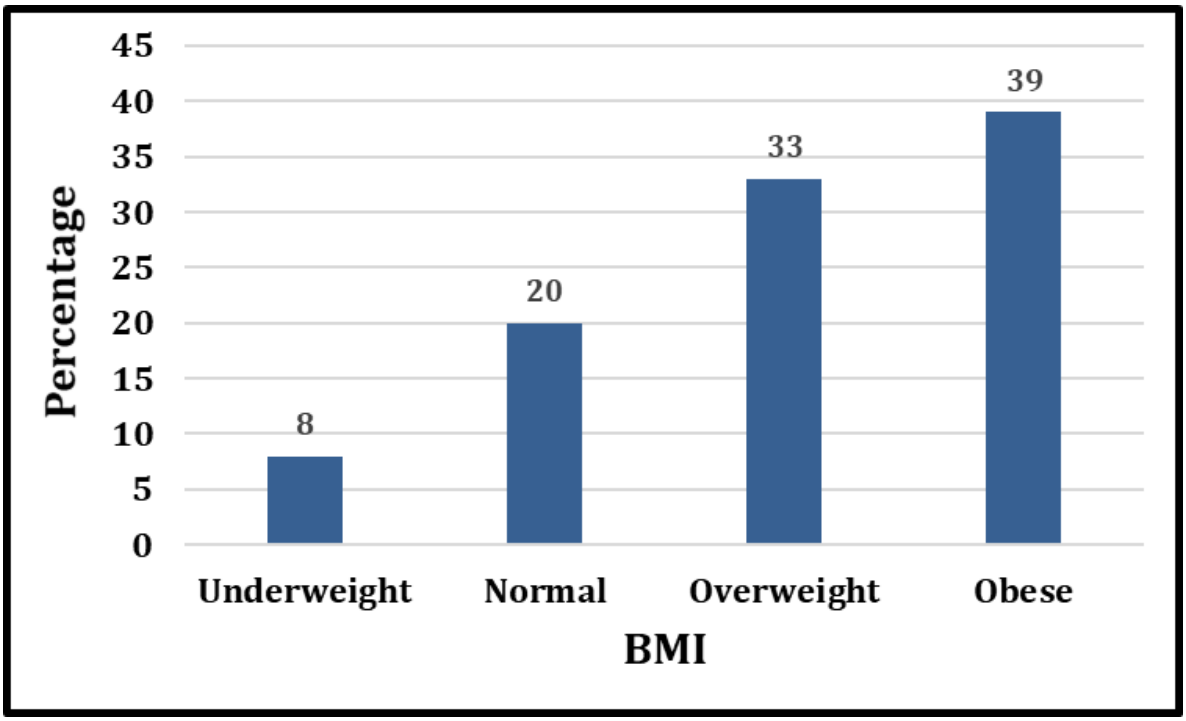

Figure 1. Classifications of women according to their BMI

This result is consistent with the finding of significantly different steroid stress profiles between pre- and postmenopausal women. Circulating cortisol and ACTH concentrations in postmenopausal women were significantly higher than those of pre-menopausal women (p= 0.02; P=0.03 respectively), which suggest that the activity of the Hypothalamic–Pituitary–Adrenal axes was increased after menopause. On the other hand, serum DHEA was markedly lower in PM with an aging and menopause related decrease of the adrenal androgen (p= 0.017). These hormonal changes also might help explain the higher frequency and severity of menopausal symptoms, psychological stress, and metabolic abnormalities observed after menopause (table 1).

Table 1. Comparison of levels of hormones between pre- and postmenopausal women

Hormones	Postmenopausal (N= 68)		Premenopausal (N= 42)		(P value)
	Mean	SD	Mean	SD	
Cortisol (µg/dL)	19.6	4.2	14.9	3.8	< 0.02 *
ACTH (pg/mL)	36.4	8.1	29.7	7.5	< 0.03 *
DHEA (µg/dL)	88.21	12.3	95.4	18.9	< 0.017 *

*** Significant at P value <0.05**

There were significant differences in the prevalence of all symptoms between PM women relative to premenopausal (PC) women. Vasomotor symptoms, sleep-related problems, mood changes and genitourinary complaints or low libido occurred significantly more often in the postmenopause. Symptom prevalence was low for pre-menopausal women, however. High chi-square values show a very strong relationship between menopausal status and the occurrence of symptoms, which in turn confirms to what extent menopause-related hormonal changes affect physical health and psychosocial condition of women (table 2).

Table 2. Comparison of symptoms between pre- and postmenopausal women

Indicators		Postmenopausal (N= 68)		Postmenopausal (N= 42)		Chi Square	P value (Sig.)
		Freq.	%	Freq.	%		
Hot Flashes	Yes	54	79.4	5	11.9	42.6	0.000 (HS)
	No	14	20.6	37	88.1		
Vaginal Dryness	Yes	49	72.1	4	9.5	41.2	0.001 (HS)
	No	19	27.9	38	90.5		
Sleep Disturbance	Yes	51	75	6	14.3	35.8	0.000 (HS)
	No	17	25	36	85.7		
Mood Disturbances	Yes	47	69.1	7	16.7	30.9	0.000 (HS)
	No	21	30.9	35	83.3		
Night Sweats	Yes	53	77.9	5	11.9	41.9	0.000 (HS)
	No	15	22.1	37	88.1		
Decrease in Libido	Yes	45	66.2	4	9.5	33.6	0.000 (HS)
	No	23	33.8	38	90.5		

Postmenopausal women reporting hot flashes had a higher average serum cortisol level than those who did not (P = 0.02), which reflects an overactivation of the HPA axis. Concentrations of cortisol also appeared to be higher among women reporting problems in sleeping (P = 0.03) and mood disturbances (P = 0.04), indicating a possible strong correlation with psychological or sleep-related menopausal symptoms and dysregulation of stress hormones. On the other hand, no significant differences were seen in cortisol levels concerning vaginal dryness (P = 0.49), night sweats (P = 0.32) and loss of libido (P = 0.13). These observations suggest that they are based on estrogen deprivation rather than cortisol-induced stress. Combined, these findings suggest gender-specific relationships between high cortisol levels and certain menopausal symptoms, most notably those pertaining to vasomotor instability, disturbed sleep and emotional control (table 3).

Table 3. Differences in cortisol according to presence of menopausal symptoms among postmenopausal women

Indicators		Cortisol (µg/dL) (N= 68)		T Test	P value (Sig.)
		Mean	SD		
Hot Flashes	Yes	18.6	4.2	2.41	0.02
	No	15.9	3.8		S
Vaginal Dryness	Yes	17.2	4	0.69	0.49
	No	16.6	3.9		NS
Sleep Disturbance	Yes	18.9	4.5	2.27	0.03
	No	16.1	3.7		S
Mood Disturbances	Yes	18.4	4.3	2.06	0.04
	No	16.2	3.8		S
Night Sweats	Yes	17.8	4.1	1.01	0.32
	No	16.9	3.9		NS
Decrease in Libido	Yes	17.6	4.2	1.52	0.13
	No	16.3	3.8		NS

Independent-samples t-test analysis showed that ACTH levels significantly differed across individual menopausal symptoms in post-menopausal women. Substances Participants experiencing hot flashes showed significantly higher ACTH levels than those without hot flashes ($t = 2.68$, $P < 0.01$), indicating augmented HPA axis activation in women with vasomotor symptoms. Among women, those with disturbed sleep had higher ACTH levels compared to nondisturbed participants ($t = 2.09$, $P = .04$), further suggesting a relationship between abnormal sleep and neuroendocrine stress reactivity. Mood disturbance was significantly different ($t = 2.39$, $P = 0.02$), Gustavsson et al., 2008, such that psychological symptoms of menopause can be associated with an increased secretion of ACTH, suggesting alterations in stress regulation and emotional processing. In contrast, vaginal dryness ($t = 1.06$, $P = 0.29$), night sweats ($t = 0.81$, $P = 0.42$), and reduced sexual desire ($t = 1.41$, $P = 0.16$) were not related to differences in ACTH levels between groups of women making it more likely that these menopausal symptoms are associated largely with peripheral estrogen deficiency than altered central HPA axis activity. In conclusion, these data suggest that ACTH is selectively associated with vasomotor and sleep and affective symptoms to conceptualize stress-related neuroendocrine pathways as API for symptom expression in menopause yet demonstrate complexity of hormonal mechanisms underpinning the menopausal syndrome (table 4).

Table 4. Differences in ACTH according to presence of menopausal symptoms among postmenopausal women

Indicators		ACTH (pg/dL) (N= 68)		T Test	P value (Sig.)
		Mean	SD		
Hot Flashes	Yes	32.6	6.8	2.68	0.01 S
	No	27.4	5.9		
Vaginal Dryness	Yes	29.8	6.4	1.06	0.29 NS
	No	28.9	6.1		
Sleep Disturbance	Yes	31.9	7.1	2.09	0.04 S
	No	28.2	5.7		
Mood Disturbances	Yes	33.1	6.5	2.39	0.02 S
	No	28.6	6		
Night Sweats	Yes	29.5	6.9	0.81	0.42 NS
	No	28.7	6.3		
Decrease in Libido	Yes	30.2	6.6	1.41	0.16 NS
	No	28.8	6.1		

Women experiencing menopausal symptoms after menopause had lower circulating levels of DHEA than those without. The decrease of DHEA was highly significant among women with decreased libido ($t = 3.54$, $P = 0.001$), stressing the androgenic role of DHEA on sexual function in postmenopausal women. Differences in vaginal dryness ($t = 2.18$, $P = 0.03$) also reached statistical significance, further implicating adrenal androgens in sustaining urogenital tissue integrity. While women experiencing hot flashes, sleep disturbance, and mood disturbances had numerically lower DHEA levels, these associations were weaker and not uniformly highlighted, suggesting that these menopausal symptoms may be primarily characterized by stress-axis activation rather than adrenal androgen insufficiency. DHEA was not meaningfully associated with night sweats ($P = 0.42$). In conclusion, the results demonstrate that DHEA deficiency is specifically associated with sexual and urogenital symptomatology, but not with global, total menopausal symptom burden (table 5).

Table 5. Differences in DHEA according to presence of menopausal symptoms among postmenopausal women

Indicators		DHEA (pg/dL) (N= 68)		T Test	P value (Sig.)
		Mean	SD		
Hot Flashes	Yes	82.4	18.6	2.72	0.01
	No	95.1	20.3		NS
Vaginal Dryness	Yes	78.6	17.9	2.18	0.03
	No	92.8	21.1		S
Sleep Disturbance	Yes	80.9	19.4	2.05	0.04
	No	93.6	22		NS
Mood Disturbances	Yes	79.2	18.1	2.41	0.02
	No	94.5	20.7		NS
Night Sweats	Yes	86.7	21.3	0.81	0.42
	No	89.4	19.6		NS
Decrease in Libido	Yes	72.5	16.8	3.54	0.001
	No	98.9	22.4		HS

Discussion

The current investigation was conducted to investigate the association of stress hormones (cortisol, adrenocorticotropic hormone [ACTH], dehydroepiandrosterone [DHEA]) with menopausal symptoms in postmenopausal women from Iraq. The results present clear patterns of neuroendocrine abnormality according to individual symptom clusters, and imply that there is more in the menopausal experience than simply sex hormone deficiency: stress axis dysregulation appears key.

The current study showed hot flashes, sleep problems and mood disorders in postmenopausal women were associated with significantly higher levels of cortisol than those not suffering these symptoms ($P < 0.05$ for all). Associations between elevated cortisol in these cohorts and higher HPA axis activity in response to somatic and emotional stressors accompanying menopause also have been reported. This confirms previous longitudinal research demonstrating elevated salivary cortisol levels through the menopausal transition (Woods, et al., 2009) and its association with symptom severity (Woods, et al., 2006). Increased cortisol has also been linked to sleep disturbances and depressive/anxious symptom in middle-aged women, further corroborating the present finding of a relationship between cortisol and complaints of sleep/mood.

of interest, cortisol did not differ significantly by vaginal dryness, night sweats or loss of libido (Yuksel et al., 2021). This pattern suggests that, although the HPA axis contributes to centrally mediated symptoms such as affect and sleep regulation, peripheral symptoms more closely linked to the estrogen deprivation state (e.g. urogenital atrophy) may function distinct from altered stress axes activity. For example, urogenital complaints have shown an association with local estrogen deficit and not stress hormones at the systemic level (Portman et al., 2014).

The relative values of ACTH generally reflected those of cortisol, although not entirely. ACTH levels were significantly higher among postmenopausal women experiencing hot flashes, sleep disturbance and mood changes compared to those who did not. ACTH is a mediator upstream of cortisol in the HPA cascade,

and its significant correlation with some key symptoms suggests an implication of central stress regulation in menopause. These findings are in agreement with the literature reporting that altered ACTH and cortisol pulsatility is linked to affective and stress-related symptoms in older persons (Kirschbaum & Hellhammer, 1994).

However, as with cortisol, ACTH did not differ significantly for vaginal dryness, night sweats, or decreased libido. At least for night sweating hot flashes, which are closely related in phenomenology, peripheral thermoregulatory changes and estrogen deprivation may contribute more than pituitary stress reactions as the lack of ACTH increase corresponding to this symptom logic. Indeed, previous studies have demonstrated that the thermoregulatory processes responsible for nocturnal sweating are not completely mediated by HPA stimulation (Freeman et al., 2005).

Levels of DHEA were significantly decreased among the postmenopausal women who reported individual symptoms (vaginal dryness and reduced libido) ($P = 0.03$ and $P = 0.001$, respectively), but not so for cortisol or ACTH. The decrease of DHEA with aging, a precursor of adrenal androgens that can be metabolically converted peripherally to estrogen and testosterone, has been reported extensively (Orentreich et al., 1984). The strong correlation between low DHEA and low libido corresponds to data on the role of adrenal androgens in female sexual desire and function during midlife (Davis et al., 2005).

Reduction in DHEA in women with vaginal dryness is also likely, as androgens have a trophic effect on urogenital tissue health (Traish et al., 2018). Notably, hot flashes, sleep disruption, mood changes or night sweats were not significantly correlated with DHEA. This implies that adrenally deficient androgens may affect sexual and genitourinary, but do not have predominant or direct effect over vasomotor and affective territories. Similarly, modest or inconsistent associations between DHEA and vasomotor symptoms have been reported by others, which underscores the complexities of menopausal symptomatology (Chua et al., 2014).

The current results provide new evidence in a Middle Eastern context, in which exposure to stressors, cultural expectations and life style factors are likely to affect the experience of menopause as well as endocrine regulation. Iraqi women may face special psychosocial stressors of gender roles in society and economic hardship with direct impact on the HPA axis following menopause. Although the evidence is scant, including studies from other than Iraq in neighboring countries has shown higher levels of stress hormones among women with high psychosocial adversity which was associated with increased somatic symptom burden (Kalesnikava et al., 2022).

The differential association of cortisol and ACTH with psychological and sleep symptoms indicates that stress-regulation interventions (CBT, mindfulness-training, life-style modification), which alleviate stress-related symptoms, may be promising for symptom relief in postmenopausal women. Increased cortisol and ACTH have additionally been associated with negative outcomes such as metabolic syndrome and cardiovascular risk. The decrease of DHEA in symptomatic women with sexological and genitourinary complaints may reinforce appropriate use for targeted androgen or local hormone treatment, however, clinical decisions should be based on patient-individualised risk-benefit calculations (Bose et al., 2009).

Limitations and Future Directions

Several limitations warrant consideration. First, a cross-sectional design does not allow us to infer causality; longitudinal studies would better address the temporal relationship between hormonal changes and symptom development. Second, the self-reported symptom-based measures have to be interpreted cautiously because of cultural reporting bias. Lastly, although the expected values utilized were derived from general endocrinology literature, replication with assay-measured hormones within this population would be ideal. Further study is needed of the interactions between stress hormones and other neuroendocrine mediators (e.g., serotonin, norepinephrine) to provide a more comprehensive understanding of integrated basis for regulation of menopausal symptoms. Moreover, clinical relevance could be enhanced with quality-of-life measurements and objective sleep/vasomotor evaluations.

Conclusion

The findings show that HPA axis functioning reflected in the high level of cortisol and ACTH as well as lower DHEA is related to core menopausal symptoms including hot flashes, sleep impairment, and mood swings, whereas low levels of DHEA are associated with sexual and genitourinary complaints in postmenopausal women. These results emphasize the intricate interaction between stress and reproductive hormone axes at menopause and support the concept of holistic clinical approaches addressing symptom domains in different ethnic populations.

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