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Assessment of serum level of prolactin, sex hormone and systemic manifestations in patients with scleroderma

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This study aimed to determine the serum levels of prolactin and dehydroepiandrosterone (DHEA) in systemic sclerosis (SSc) and their correlation with disease duration and clinical manifestations. This case control study investigated 26 scleroderma patients and 26 healthy individuals adjusted for age and sex with the case group as controls. Serum levels of DHEA using radioimmunoassay (RIA) and prolactin using immune radiometric assay (IRMA) were measured in both groups. Clinical manifestations of the disease, disease duration, and fertility status at the time of the study were also determined for each scleroderma patient. The findings on 26 scleroderma patients (20 females and 6 males with mean age of 44 years and mean disease duration of 5±3 years) demonstrated that serum levels of DHEA were significantly lower in scleroderma patients than controls based on gender (males, p= 0.02) and fertility (fertile women, p= 0.01; menopausal women, p= 0.008). However, no significant difference was found in prolactin serum levels between the case and control groups. Moreover, only serum PRL levels correlated significantly with disease duration in fertile women. Contrary to previous studies, this study manifested that serum PRL did not differ between scleroderma patients and normal individuals. Yet, serum DHEA was shown to be significantly lower in scleroderma patients. Only PRL levels correlated significantly with disease duration.

Keywords: DHEAS, prolactin, scleroderma, sex hormone, systemic sclerosis.

Introduction

Systemic sclerosis (SSc) is an autoimmune disease with unknown etiology. It is characterized by excessive fibrosis of the skin and other internal organs following immune system dysfunction [1-3].

To maintain hemostasis in the body, a balance must be established between the neuroendocrine and immune systems [2,4]. Some previous studies have indicated the possible role of hypothalamic-pituitary-adrenal axis (HPA) disorders and alteration of androgen metabolism in the pathophysiology of scleroderma [5,6].

DHEA, produced abundantly by human adrenal glands, was found to be a regulatory factor for releasing pro-inflammatory cytokines such as interleukin 1 (IL-1), IL-2, and IL-6 and tumor necrosis factor α (TNFα) [8,10, 12].

Moreover, prolactin, a major hormone produced by hypothalamic-pituitary-adrenal axis (HPA), is known to be a lactogenic hormone secreted by the anterior pituitary gland; however, it can also be synthesized in various extra-pituitary sites such as the decidua, prostate, neurons, skin, immune cells, and mammary epithelium [4,9]. According to previous studies, in addition to its major role in reproduction, it is also capable of participating in the immune system [4,7,13]. This hormone can affect immune cells by stimulating the activation and proliferation of T cells and the production of TNF α, interferon γ (IFN γ), IL-1β, and IL-12 [4,7,11]. It has further been suggested that Prl can negatively affect the immune tolerance through regulatory T-cell suppression [14].

Previous studies have revealed high serum prolactin levels as well as low serum DHEA levels in both women and men with autoimmune diseases [7,8,15]; however, there can be found no study which compares the serum levels of these hormones in scleroderma patients with healthy individuals. Thus, the current study purposed to assess the serum levels of PRL and DHEA in scleroderma patients and compare them with healthy individuals in a control group. Furthermore, the correlation of these hormones with disease duration and clinical manifestations was also investigated in this study.

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Materials and Methods

Study design

This case control study was performed on scleroderma patients referring to the Tertiary Center of Rheumatology in Hafez Hospital, Shiraz University of Medical Sciences, Shiraz, Iran. Twenty-six scleroderma patients whose diagnosis was based on American College of Rheumatology (ACR) criteria were recruited in this study. Moreover, 21 healthy individuals adjusted for gender and age with the case group were also entered into the study as the control group.

Ethical approval for this study was obtained from the Ethics Committee of Shiraz University of Medical Sciences as per the Helsinki guidelines [16].

Female patients with a history of pregnancy and breast-feeding and ones with prolactinemia, hypothyroidism, or renal failure were excluded from this study. Moreover, individuals who took hormone-altering medications, such as corticosteroids and oral contraceptive pills, were also excluded [2,8,17].

Measurements

Data on the patients' clinical manifestations was gathered by reviewing documents in the scleroderma clinic and entering it into prepared data-gathering sheets.

The serum levels of DHEAS and prolactin were measured in both case and control groups. Blood samples were taken at 8-10 a.m. from participants in the fasted state. The serum was separated and incubated in -80°C. DHEAS was measured by radioimmunoassay (RIA) (Aria Pharmed Trade Co., Iran) and prolactin levels by immunoradiometric assay (IRMA) (Padyab Teb Co., Iran).

The results were compared between the case and control groups. All hormonal tests were performed in the endocrine and metabolism research center with a Gamma counter instrument (Kontron, made by Austria) which was calibrated regularly by the local representative company in Iran.

Statistical methods

All statistical analyses were performed using Statistical Analysis Package for Social Sciences, version 18 (SPSS, Inc., Chicago, IL, USA) [18]. The Mann-Whitney U test was used to compare the differences in serum levels of hormones between case and control groups. In addition, linear regression was applied to detect the relationship between hormones (DHEAS and Prl) as the dependent variable and disease duration as the independent variable. The component of β (coefficient beta) in the standardized linear regression was utilized to discern the strength of interrelation. Data was reported as means±SD for 95% CI with 5% degree of freedom. A $p<0.05$ was considered statistically significant.

Results

The mean age of the scleroderma patients was 36.6±1.47 years in fertile females and 53.2±2.46 in post-menopausal females.

Statistical analysis revealed that DHEAS in childbearing females ($p=0.01$), postmenopausal females ($p=0.008$), and males ($p=0.026$) were significantly lower compared with healthy individuals. However, the level of Prl was not significantly different in either SSc patients or controls.

The results revealed that there was no significant association between hormone levels and disease manifestations based on gender. The linear regression results showed that the serum level of Prl had a significant relationship with disease duration in fertile females ($p=0.023$). The interpretation of β predicted the amount of change in the dependent variable, showing that individuals who had a beta coefficient of 0.548, for every unit change in disease duration there was a 0.548-unit increase in the serum level of Prl (Fig. 2). As for the remaining individuals (males and postmenopausal females), further linear regression analyses were not able to predict any connection between disease duration and hormone activities (Figs. 3 & 4).

Discussion

Despite many studies on the pathophysiology of scleroderma, its etiology is still obscure. Some studies have suggested the possible role of a hormonal imbalance in the pathogenesis of this disease. However, there are many controversies regarding the role of hormones in SSc. Among the investigated hormones, DHEA and PRL were the most common ones revealed to play a role in scleroderma. Nevertheless, no definite result can be obtained through a literature review.

The current results demonstrated that serum levels of DHEAS were significantly lower in scleroderma patients compared with the controls; this confirmed the results reported by Luisa Mirone et al., Richard Imrich et al., and Straub et al.

Previous studies have proposed that age and depression are major factors contributing to low serum DHEA levels. However, the current results on the relationship between serum hormonal levels and SSc clinical manifestations did not show any significant correlation between these two variables. Furthermore, DHEA was shown to have anti-inflammatory functions.

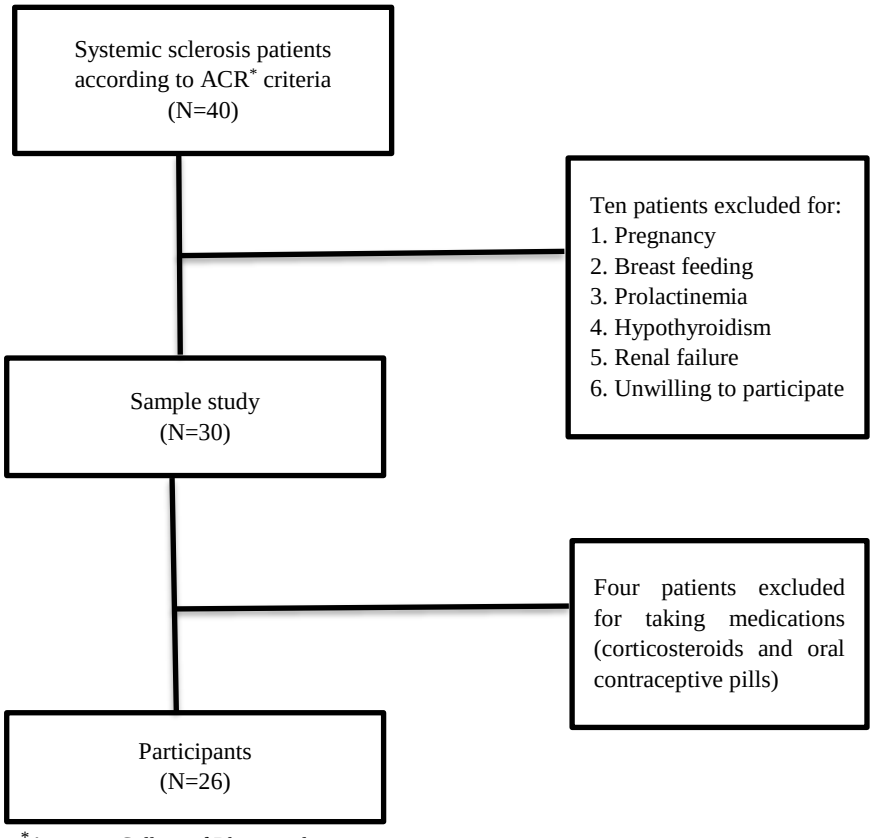
This finding reinforces the role of low serum DHEA levels in the pathogenesis of scleroderma.

Previous investigations have dealt with acute stressful conditions (i.e. hypoglycemia) to examine the hypothalamus-pituitary-adrenal (HPA) axis function in SSc patients [2], but the implementation of such approach revealed no significant changes in DHEAS levels regarding acute stress [25]. According to the statements above, the type and degree of stress can simply influence the regulation of body systems in a different way. Thus, the mechanism which led to a reduction of DHEAS in subjects of the current investigation may be attributed to the type (continuous) of stress that is a chronic disease. This can also be explained when inflammatory cytokines and/or any other trigger factor which play a role in this disease generates a continuous stimulus on the HPA axis and promotes further reduction in DHEAS [26].

Such contrast may be due to therapeutic effects which were able to control the inflammatory reaction.

The current data indicated that there was a direct interrelation between the serum level of Prl and disease duration in fertile females. Prl was shown to be essential for normal reproduction. Moreover, it was also found that the fertility of SSc patients does not differ with that of the normal population [27,28]. It seems that an adaptive response occurred in female scleroderma patients, which preserves fertility in these patients. According to the data, females with a prolonged disease duration were able to sustain higher Prl levels in their blood, but the Prl was not high enough to cause amenorrhea. These findings also suggested a difference in the endocrine behavior of male and female patients regarding Prl levels. No studies were found which reported higher levels of PRL in scleroderma patients.

The review of previous studies drew the authors to conclude that there can be a positive correlation between serum levels of Prl and DHEAS and age and gender [8, 29-32]. Nonetheless, the current results revealed that there is no relationship between the clinical manifestations of SSc and serum levels of hormones.



*American College of Rheumatology

Fig. 1. The number of participants, excluded and included participants

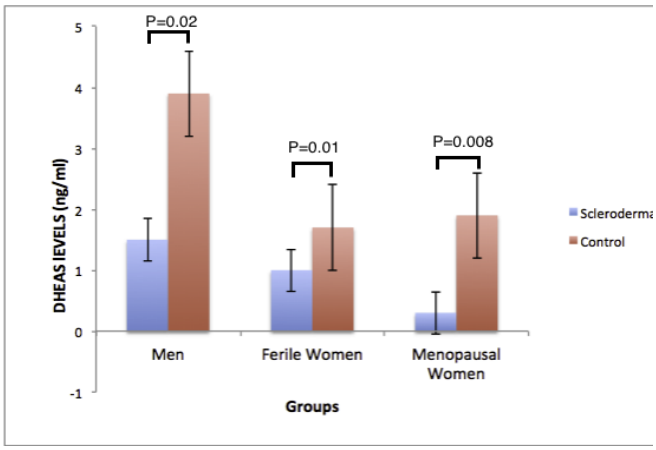


Fig. 2. Comparing levels of dehydroepiandrostrone (DHEA) between groups based on sex and fertility

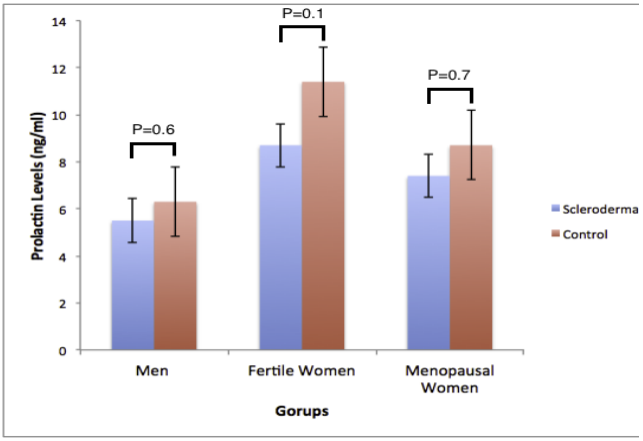


Fig. 3. Comparing levels of prolactin (PRL) between groups based on sex and fertility

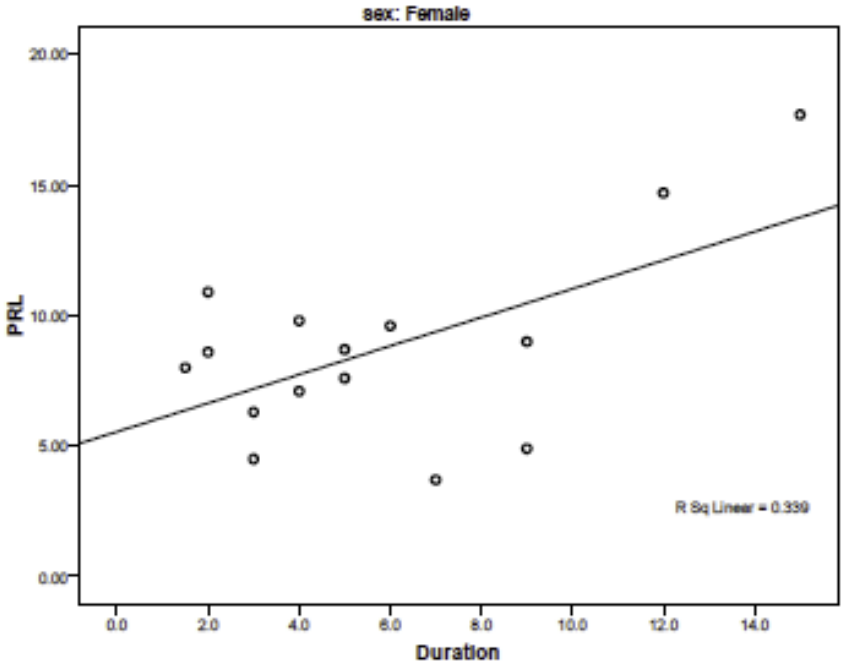


Fig. 4. Correlation of serum prolactin levels of fertile women and disease duration

In conclusion, it was detected that DHEAS hormone levels were considerably lower in patients with SSc. In contrast, levels of the Prl hormone remained unchanged as compared with the controls. The results also indicated that there is no association between the basal plasma level of such hormones and systemic manifestations of SSc in the subjects.

Limitations of the study

Although this research was carefully prepared, it does have some limitations. The population of the study is small due to financial limitations. Also, a lack of time was a big constraint on this study.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

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