Comparison of Serum Level of Sex Hormones in Patients with Frontal Fibrosing Alopecia with Control Group

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ABSTRACT

Context: Although etiopathogenesis of frontal fibrosing alopecia (FFA) is not fully discovered, it seems that hormonal factors play a role. Aims: The aim of this study was to investigate the serum level of sex hormones in patients with FFA compared to a control group.

Settings and Design: This was a case–control study. Subjects and Methods: All patients who referred to the Dermatology Clinic of Faghihi Hospital, Shiraz University of Medical Sciences, between 2013 and 2018 and were pathologically and clinically diagnosed with FFA were considered as the case group. The control group was selected from community people who did not have alopecia, and each was matched with its counterpart in the case group in terms of gender, age, and menstrual status. Both the groups were evaluated for serum level of sex hormones. Statistical Analysis Used: SPSS software version 23 was used in this study.

Results: Of 20 patients, who were all female, 8 were postmenopausal and 12 were cyclic. There was no significant difference between sex hormone levels of the case and control groups regardless of their menstrual statuses. Similarly, there was no significant difference between hormonal levels in postmenopausal women of both the groups. However, follicle-stimulating hormone (FSH) was significantly lower in the case group cyclic women. Moreover, postmenopausal patients with premenopausal onset of FFA had lower levels of FSH and luteinizing hormone than those with postmenopausal onset. Free testosterone correlated inversely with duration of FFA.

Conclusions: It seems that the pathogenesis of FFA is not associated directly with serum concentrations of sex hormones. Therefore, future studies are recommended to investigate possible tissue mechanisms of hormonal factors involved in its pathogenesis.

Key words: Alopecia, etiology, gonadal steroid hormones, postmenopause

INTRODUCTION

Frontal fibrosing alopecia (FFA) is a progressive cicatricial alopecia that is featured by recession of hairline in the frontotemporal region. Although it was primarily introduced in postmenopausal women, there are increasing reports demonstrating the incidence of FFA in cyclic women and also in men.[3-5] Even its incidence has been reported in pediatric cases.[8] Since its introduction by Kossard in 1994, the mechanisms of etiopathogenesis of FFA have not yet been fully understood. However, it seems that there are four categories of immune-related, genetic, hormonal, and environmental factors involved in its pathogenesis.[3,7]

There is much evidence in literature revealing the role of hormonal factors in pathogenesis of FFA. FFA mainly occurs in postmenopausal women, and interestingly, early menopause has been reported in them more than general population.[3,8] Moreover, 5-alpha-reductase inhibitors

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How to cite this article: Sasannia M, Saki N, Aslani FS. Comparison of serum level of sex hormones in patients with frontal fibrosing alopecia with control group. Int J Trichol 2020;12:1-6.
are among the most effective therapies used in the treatment of FFA, another finding in favor of hormonal mechanisms involved in the disease. In addition, some studies have shown a considerable coexistence of FFA with androgenetic alopecia (AGA), and we are aware of the role of androgens in pathogenesis of AGA. On the other hand, Buendía-Castaño et al. conducted a case-control study on hormonal and gynecological risk factors of FFA, showing that the case group had an age of menopause 2 years earlier than that of the control group, and the intake of tamoxifen was a risk factor for FFA while intrauterine device usage was a protective factor. Another study demonstrating the role of hormonal exposure in pathogenesis of FFA was conducted by Moreno-Arrones et al. which considered pregnancy, use of raloxifene, and hormone replacement therapy as significant risk factors in the case group.

The evidence supporting hormonal mechanisms in the pathogenesis of FFA raises the question whether blood levels of sex hormones in patients with FFA differ from normal population. To investigate the answer, Bernárdez et al. conducted a study on premenopausal women with FFA, which did not show any abnormalities in their sex hormones. However, postmenopausal women were not studied in this research.

In this study, we investigated serum levels of sex hormones in both postmenopausal and cyclic women with FFA in comparison with a control group.

**SUBJECTS AND METHODS**

In this case-control study, all the patients who referred to the Dermatology Clinic of Faghihi Hospital affiliated with Shiraz University of Medical Sciences, Shiraz, Iran, between 2013 and 2018 and were pathologically and clinically diagnosed with FFA were considered as the case group. To find the patients, we searched the pathology archives of the hospital and found 42 reports in the mentioned years which had a diagnosis of FFA. To confirm the diagnosis, the patients were invited to the Dermatology Clinic to be examined by our dermatologist. Twenty-five of 42 patients came to the clinic, and FFA was confirmed in 22 patients. Patients who did not cooperate, had active hormonal therapy, or were pregnant or breastfeeding were excluded from the study. Finally, according to the inclusion and exclusion criteria, twenty patients were considered as the case group. Control group members were selected with a proportion of one to one from the people of the community who did not have alopecia (based on physician’s examination), did not have active hormonal therapy, and were not pregnant or lactating, and each of them was matched with its counterpart in the case group in terms of gender, age (±4), and menstrual status. After selection of the members of the case and control groups, they were evaluated for serum level of sex hormones including dehydroepiandrosterone sulfate (DHEAS), testosterone (total and free), prolactin, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). They were informed about the pretest preparations, and the cyclic women of both the groups were told to do the tests on the 3rd–5th day of menstruation period. For assessment of the hormones, 8 ml of their blood (clot sample) was gathered. Radioimmunoassay was used for measuring DHEAS by a standard kit (DHEA-SO\textsubscript{11–125} RIA Kit, Institute of Isotopes Company, Hungary) and total testosterone by another standard kit (Testosterone RIA CT – 100 tubes, Cisbio Company, The Netherlands). Immunoradiometric assay was used for measuring LH (LH IRMA Kit 100 Tests, Padtan Gostar Isar Company, Iran), FSH (FSH IRMA Kit 100 Tests, Padtan Gostar Isar Company, Iran), and prolactin (PRL IRMA Kit 100 Tests, Padtan Gostar Isar Company, Iran). Furthermore, free testosterone was measured by enzyme-linked immunosorbent assay with a standard kit (Free Testosterone AccuBind ELISA Kit – 96 wells, Monobind Company, USA).

After collecting the information, in addition to descriptive statistics, due to the low number of the patients, we used the nonparametric test of Mann–Whitney by SPSS software version 23 (IBM Corporation, Armonk, New York, USA) to compare the quantitative data between the case and control groups and bivariate correlation of Spearman to analyze the relationship between sex hormone levels and duration of the disease. $P < 0.05$ was considered as statistically significant.

This study was in accordance with the ethical standards of the Institutional and National Research Committee (School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran, with approval ID: IR.SUMS.MED.REC.1397.231) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all individual participants included in the study.

**RESULTS**

There were 40 participants, 20 of whom were considered as the case group with a mean age of 46.9 years, ranging from 33 to 65 with standard deviation (SD) of 10.8 [Table 1].
Furthermore, the control group consisted of 20 participants with a mean age of 47.20 years (range: 33–69, SD: 11.5). All the participants were female.

In the case group, 8 participants were postmenopausal and 12 were cyclic [Table 1]. Due to the matching of the case and control groups in terms of age, menstrual status, and sex, this proportion was the same in the control group in terms of menstrual status. Of the eight postmenopausal women in the case group, six presented the disease after the onset of menopause, while the onset of the disease in two other women was before menopause.

In comparison of the six hormones studied in the case and control groups regardless of menstrual status, no significant differences were observed between the case and control groups as shown in Table 2.

Furthermore, the levels of these hormones were compared in cyclic participants of both the groups, and no significant differences were seen between them except for FSH [Table 3]. The serum level of FSH (IU/L) in cyclic women of the case group (9.00, 11.20) showed a significant difference compared to their matches in the control group (15.11, 15.65) with \( P = 0.03 \).

The same comparison was done for postmenopausal individuals of both the groups which did not reveal any significant differences between them. The results are followed in Table 4.

As mentioned above, in the postmenopausal women of the case group, the onset of the disease was after the beginning of menopause in six individuals and before menopause in two others. We compared serum levels of sex hormones between these two groups [Table 5]. The serum level of LH (IU/L) in individuals who contracted the disease after menopause (38.09, 14.20) in comparison with the ones who presented the disease before menopause (19.70, 1.84) demonstrated a significant difference \( (P = 0.04) \). Regarding FSH levels (IU/L), individuals who presented the disease after menopause (55.27, 10.85) demonstrated a significant difference in comparison with the ones who caught the disease before the onset of menopause (36.72, 7.13) with \( P = 0.04 \). The comparison of other four hormones did not show a significant difference.

In the present study, the patients had been suffering from FFA for different durations, ranging from 1 to 23 years [Table 1], averagely 5.4 years (SD: 4.9). However, the serum level of sex hormones other than free testosterone did not have a significant relationship with duration of the disease in the cyclic and postmenopausal women separately and also in all patients generally. It is while the serum level of free testosterone was shown to decrease as the duration of the disease increased in the patients generally (correlation coefficient: \( -0.53, P = 0.02 \)), although this correlation was not significant in the subgroups (cyclic women and the postmenopausal ones) separately [Table 6].

**DISCUSSION**

FFA is a scarring alopecia, the etiology of which is not fully explained since its introduction in 1994. However, it is assumed that immune-related, genetic, hormonal, and environmental factors play a role in its pathogenesis.\(^3,7\) In the current study, we focused on the role of serum level of sex hormones in the development and progression of the disease.

The comparison of the level of sex hormones between the case and control groups regardless of menstrual status did not reveal any significant differences, which can be partly due to the small sample size of the study. Regarding different levels of sex hormones between cyclic and postmenopausal women, we also compared serum levels of sex hormones...
Table 2: Serum level of sex hormones in the case and control groups regardless of menstrual status

| Hormone            | Group   | Minimum | Maximum | Mean   | SD     | P  |
|--------------------|---------|---------|---------|--------|--------|----|
| LH (IU/L)          | Case    | 0.49    | 60.83   | 17.24  | 17.06  | 0.51|
|                    | Control | 2.04    | 59.91   | 20.41  | 18.68  |    |
| FSH (IU/L)         | Case    | 2.31    | 76.52   | 25.65  | 23.90  | 0.26|
|                    | Control | 4.89    | 68.14   | 29.13  | 22.87  |    |
| Prolactin (ng/mL)  | Case    | 5.30    | 65.20   | 15.65  | 14.34  | 0.42|
|                    | Control | 5.10    | 72.20   | 17.13  | 14.96  |    |
| Total testosterone (ng/mL) | Case | 0.18    | 0.80    | 0.39   | 0.15   | 0.30|
|                    | Control | 0.28    | 0.57    | 0.39   | 0.06   |    |
| Free testosterone (pg/mL) | Case | 0.36    | 2.90    | 1.06   | 0.60   | 0.42|
|                    | Control | 0.48    | 2.88    | 1.29   | 0.70   |    |
| DHEAS (µg/dL)      | Case    | 15.00   | 107.00  | 114.42 | 60.42  | 0.06|
|                    | Control | 30.00   | 150.00  | 127.25 | 89.99  |    |

SD – Standard deviation; LH – Luteinizing hormone; FSH – Follicle-stimulating hormone; DHEAS – Dehydroepiandrosterone sulfate

Table 3: Serum level of sex hormones in the cyclic women of the case and control groups

| Hormone            | Group   | Minimum | Maximum | Mean   | Reference range* | SD     | P  |
|--------------------|---------|---------|---------|--------|------------------|--------|----|
| LH (IU/L)          | Case    | 0.49    | 25.52   | 6.40   | 1.0‑7.9          | 6.67   | 0.52|
|                    | Control | 2.04    | 44.55   | 9.72   | 12.32            | 11.20  |    |
| FSH (IU/L)         | Case    | 2.31    | 43.87   | 9.00   | 2.5‑13.2         | 11.20  | 0.03|
|                    | Control | 4.89    | 55.16   | 15.11  | 18.69            | 15.65  |    |
| Prolactin (ng/mL)  | Case    | 7.70    | 65.20   | 19.88  | 1.0‑30           | 18.28  | 0.44|
|                    | Control | 7.70    | 72.20   | 20.63  | 18.69            | 18.69  |    |
| Total testosterone (ng/mL) | Case | 0.18    | 0.80    | 0.42   | 0.07‑1.22        | 0.19   | 0.58|
|                    | Control | 0.29    | 0.57    | 0.40   | 0.06             | 0.40   |    |
| Free testosterone (pg/mL) | Case | 0.56    | 2.90    | 1.28   | 0.4‑7.1          | 0.72   | 0.48|
|                    | Control | 0.52    | 2.88    | 1.57   | 0.84             | 0.84   |    |
| DHEAS (µg/dL)      | Case    | 40.00   | 267.00  | 123.87 | 30‑333           | 62.73  | 0.20|
|                    | Control | 74.00   | 301.00  | 172.75 | 87.56            | 87.56  |    |

*In accordance with reference ranges for cyclic women (at follicular phase for LH and FSH); †Statistically significant. SD – Standard deviation; LH – Luteinizing hormone; FSH – Follicle-stimulating hormone; DHEAS – Dehydroepiandrosterone sulfate

Table 4: Serum level of sex hormones in the postmenopausal women of the case and control groups

| Hormone            | Group   | Minimum | Maximum | Mean   | Reference range* | SD     | P  |
|--------------------|---------|---------|---------|--------|------------------|--------|----|
| LH (IU/L)          | Case    | 18.40   | 60.83   | 33.49  | 3.1‑41.0         | 14.73  | 0.60|
|                    | Control | 13.43   | 59.91   | 36.43  | 14.82            |        |    |
| FSH (IU/L)         | Case    | 31.68   | 76.52   | 50.63  | 32‑126           | 12.85  | 0.91|
|                    | Control | 27.67   | 68.14   | 50.17  | 13.89            |        |    |
| Prolactin (ng/mL)  | Case    | 5.30    | 15.10   | 10.36  | 2.0‑15.0         | 3.53   | 0.75|
|                    | Control | 5.10    | 26.50   | 12.77  | 7.44             |        |    |
| Total testosterone (ng/mL) | Case | 0.27    | 0.43    | 0.34   | 0.07‑1.22        | 0.05   | 0.42|
|                    | Control | 0.28    | 0.48    | 0.37   | 0.06             |        |    |
| Free testosterone (pg/mL) | Case | 0.36    | 1.33    | 0.81   | 0.4‑7.1          | 0.33   | 0.52|
|                    | Control | 0.48    | 1.50    | 0.97   | 0.31             |        |    |
| DHEAS (µg/dL)      | Case    | 15.00   | 86.00   | 57.25  | 32‑205           | 26.15  | 0.15|
|                    | Control | 30.00   | 172.00  | 91.87  | 51.14            |        |    |

*In accordance with reference ranges for postmenopausal women. SD – Standard deviation; LH – Luteinizing hormone; FSH – Follicle-stimulating hormone; DHEAS – Dehydroepiandrosterone sulfate
lower in postmenopausal women with premenopausal onset in comparison with the ones with postmenopausal onset of FFA, while the levels of these hormones were within normal ranges. Further studies with larger sample sizes are recommended to answer this question.

Regarding the evidence in literature in favor of hormonal mechanisms in pathogenesis of FFA in conjunction with the observation that the patients have normal levels of sex hormones in their blood, it seems that hormonal factors play a role in the pathogenesis of FFA by local mechanisms, not necessarily directly by their blood concentrations, as Gaspar mentioned in a review article that a decrease in local activity of dehydroepiandrosterone might have an association with follicular fibrosis.[15]

In addition to the normal mean sex hormone levels of the patients, it appears that the duration of the disease does not affect hormonal levels (except free testosterone which inversely correlates with duration of FFA). However, it is possible that hormones have variations in their blood levels in conjunction with different phases of the disease, not solely with its duration, as it was found in a study on oral lichen planus that the level of prolactin had decreased in the remission phase compared to the exacerbation phase.[16]

Finally, this study was not free from some limitations. It had a small sample size due to the low number of patients, and all the patients were female. We did not have any men diagnosed with FFA. In addition, the levels of the hormones at the onset of the disease were not available, although it seems that the levels of most of the hormones are not affected by the duration of FFA. Thus, future studies are suggested with larger sample sizes including men, evaluating the levels of the hormones (including the ones we studied and also other hormones, such as estrogen, progesterone, and dihydrotestosterone) at the beginning and different phases of the disease.

**CONCLUSIONS**

It seems that the pathogenesis of FFA is not associated directly with serum concentrations of sex hormones. Therefore, future studies are recommended to investigate possible tissue mechanisms of hormonal factors involved in pathogenesis of the disease.
Acknowledgment

The current article was extracted from the thesis by Mohammad Sasannia, which was financially supported by Shiraz University of Medical Sciences, Shiraz, Iran (Grant number: 1396-01-01-16571).

Financial support and sponsorship

This study was funded by Shiraz University of Medical Sciences, Shiraz, Iran (Grant number: 1396-01-01-16571).

Conflicts of interest

There are no conflicts of interest.

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