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Free Androgen Index (FAI): Marker of Premature Androgenetic Alopecia in Men

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Abstract

Introduction: Premature androgenetic alopecia (AGA) in men is alopecia occurring before the age of 30 years. We conducted this study to evaluate various androgenic hormones in men with premature androgenetic alopecia and to assess if free androgen index (FAI) can be used as a marker of hyperandrogenism in these men.

Materials and methods: 57 men with premature AGA (defined as grade 3 or more on Hamilton-Norwood scale) were taken as subjects. The serum concentrations of Testosterone, DHEAS, and SHBG were measured and Free androgen index (FAI) was calculated and compared with age and sex matched controls.

Results: There were significant differences in the mean values of all the three indicators for androgen status (FAI, DHEAS and testosterone) in cases as compared to the controls. The statistical significance was higher for FAI and DHEAS than that for testosterone. FAI appeared to be a better predictor of hyperandrogenism than DHEAS and testosterone.

Conclusion: FAI is the best marker of a person's androgen status and can be considered as the marker of premature AGA. Taking into consideration the technical limitations of the currently available methods for measuring free testosterone, and the diagnostic importance of using FAI as indicator of androgen status, it is recommended to implement these parameters in the routine investigation and assessment of men with AGA.

Keywords: Free androgen index; Androgenetic alopecia; Testosterone

Introduction

Patterned hair loss also known as androgenetic alopecia (AGA), is a hereditary androgen dependent disorder characterised by a progressive process that causes a gradual conversion of terminal hair into miniaturized hair defined by various patterns [1]. It is a feature of men who have sufficient circulating androgens. Male pattern hair loss is characterised by its typical bitemporal recession of hair and balding vertex [2]. Premature patterned hair loss is hair loss occurring before the age of 30 [3].

AGA is a state of hyperandrogenemia. It occurs due to interplay between various hormones like Total testosterone, Sexual hormone binding globulin, Dihydroepiandrosterone (DHEAS), Leutinizing hormone and Follicle stimulating hormone. Free testosterone and Free Androgen Index (FAI) seem to be sensitive for the detection of hyperandrogenemia. FAI is the total testosterone level divided by the sex hormone binding globulin (SHBG) level, and then multiplying by a constant, usually 100. The majority of testosterone in the blood does not exist as the free molecule. Instead around half is tightly bound to sex hormone binding globulin, and the other half is weakly bound to albumin. Only a small percentage is unbound, under 3% in females, and less than 0.7% in males [4]. Since only the free testosterone is able to bind to tissue receptors to exert its effects, it is believed that free testosterone is the best marker of a person's androgen status. However, free testosterone is difficult and expensive to measure, and many laboratories do not offer this service. We conducted this study to compare the levels of various androgenic hormones (Total testosterone, SHBG, DHEAS) and FAI in men with premature androgenetic alopecia in comparison to that in men without any alopecia.

Materials and Methods

A case-control study approved by the Institutional Ethics Committee was carried out at tertiary hospital. Fifty seven males aged 19-30 years presenting with patterned hair loss (defined as grade 3 or more on the alopecia classification scale of Hamilton with Norwood modification) were taken as study subjects [5,6]. Thirty two age matched males with no evidence of hair loss were taken as controls. Men who had any established endocrine disorder, diabetes mellitus or cardiovascular disease and those who took any oral medication or hormonal treatment for hair loss were excluded from the study.

Detailed anamneses were recorded for each individual. All participants were assessed by the same physician. Total testosterone, sex hormone-binding globulin (SHBG) and DHEAS of the patients were obtained from blood samples drawn after an 8-hour fast in the morning between 8 am to 9 am and analyzed.

DHEAS and SHBG were estimated by ELISA and testosterone was assayed by Electro-Chemiluminescent immunoassay. Free androgen index was calculated using the formula: $Testosterone\ (nmol/L) \times 100 / SHBG\ (nmol/L)$ [7].

Statistical analysis

The results were analyzed using SPSS software version 20. Mean and standard deviation were calculated for continuous parameters. Unpaired

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student's t-test / ANOVA test were used to compare quantitative variables and Chi-square test was used to compare qualitative variables. p value <0.05 was considered to be statistically significant.

Results

All participants of the study were below 30 years of age. The mean age of cases was 24.7 ± 2.8 years and that of controls was 24.2 ± 2.6 years. The hormone profile of cases and controls are given in Table 1.

There was no statistically significant association between severity of grades of AGA (Grade III, IV, V, VI and VII) with the various hormone levels.

Discussion

Androgenetic alopecia occurs due to interplay between androgens and genetics. Evaluating hormones derived from testis, adrenals as well as pituitary gland in these men is essential to get closer to the etiopathogenesis of premature AGA and also for the management. The pilosebaceous unit synthesizes and metabolizes a wide range of androgens like testosterone and other weaker androgens such as dehydroepiandrosterone [8]. The dermal papilla is considered the main site of androgenic action and, in response to androgens it could alter the production of soluble regulatory factors that influence the growth and activity of hair follicle keratinocytes [9]. Systemically produced androgens also enter the hair follicle through passive diffusion.

Locally and systemically derived testosterone either directly binds to intracellular androgen receptors mainly expressed within the dermal papilla and hair bulb or is metabolized into the more potent dihydrotestosterone (DHT), which, in turn, binds to androgen receptors(AR) with an approximate fivefold greater affinity [10]. The conversion of testosterone to DHT in hair follicles is predominantly mediated by the 5a-reductase Type II enzyme. It is thought that DHT is the key androgen required for the induction of male pattern hair loss [10].

In the current study, there were significant differences in the mean values of all the three indicators for androgen status (FAI, DHEAS and testosterone) in cases compared to the controls. The statistical significance was higher for FAI and DHEAS than for testosterone. FAI and DHEAS appeared to be better predictors of hyperandrogenism than testosterone.

In our study, the mean value of testosterone in cases was significantly higher as compared to controls in agreement with studies by Narad et al. [11], Schmidt et al. [12] and Yildiaz et al. [13]. However, Duskova et al. [14] and Starka et al. [15] showed subnormal levels of testosterone in their cases. Increased levels of testosterone, leads to increased dihydro-testosterone by 5 α reductase and thus increased action of these androgens on the dermal papillae cells of hair follicle, in these patients. AGA in patients with normal testosterone levels could be attributed to increased androgen receptors, or increased androgen sensitivity.

The mean DHEAS levels were significantly increased in our cases similar to Duskova et al. [14] and Legro et al. [16]. However, Narad et al. [11] and Schtmidt et al. [12] found normal values of DHEAS in their studies. Increased levels of DHEAS indirectly point towards increased androgens. These result in premature balding by acting on the dermal papillae cells.

Parameters	Normal range	Cases (mean ± SD)	Controls (mean ± SD)	p value
Testosterone levels	10-34 nmol/L	24.61 ± 7.97	20.57 ± 4.93	0.04
DHEAS levels	0.9-3.6 µg/ml	4.47 ± 1.23	3.12 ± 0.89	0.03
SHBG levels	15-100 nmol/L	35.07 ± 11.11	46.41 ± 14.03	0.00
Mean FAI levels		74.49 ± 38.20	49.99 ± 23.17	0.00

Table 1: Comparison of hormonal parameters between cases and controls (p < 0.05 is Significant).

The mean value of SHBG in cases was significantly lower as compared to controls. Similar findings were noted by Duskova et al. [14] and Narad et al. [11] lower the levels of SHBG, higher the free testosterone and thus hyperandrogenism.

In our study, the mean FAI was higher in cases as compared to controls which were highly significant. FAI is homologous to free testosterone which is not bound to albumin or to SHBG, and is freely available for action at the tissue level. Free testosterone accelerates gradual transformation of large terminal scalp follicles to tiny villous ones causing premature AGA in genetically predisposed person. At least 80% of bound serum testosterone is bound to SHBG. Consequently, free serum testosterone levels are substantially influenced by SHBG levels, which limit the interpretation of free serum testosterone. FAI takes this SHBG dependence into account. This shows that FAI is the best marker of a person's androgen status as it can bind to tissue receptors.

Conclusion

Taking into consideration the high prevalence of androgen excess status in men with premature AGA, the known technical limitations of the currently available methods for measuring free testosterone, and the diagnostic improvement when using FAI as indicators of androgen status, it is highly recommended to implement these calculated parameters in the routine investigation and assessment of men with AGA. For this approach, assessment of androgen status should include measurement of both total testosterone and SHBG, and based on their values, calculation of FAI can be obtained and reported as a profile. This will improve the diagnostic efficiency of testosterone in diagnosing hyperandrogenism. The FAI may be a cost-effective alternative to free Testosterone measurement for the management of AGA.

There were few shortcomings in our study such as small sample size. Large multicentric studies should be undertaken to study the endocrinological profile in premature AGA. Sequential follow up of these men should be undertaken for next two decades, to know about the changing hormonal profile with increasing age.

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