Early Androgenetic Alopecia and Insulin Resistance- A case control study

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Abstract

Background: In Androgenetic alopecia AGA, androgens induce miniaturization of hair follicles in those genetically predisposed to baldness. The previously known association between Androgenetic Alopecia AGA and cardiovascular risk factors raises a question of common pathogenetic mechanism of these disorders.

Aim: To study the association of Insulin resistance and metabolic syndrome in early onset AGA in young males

Materials and Methods: This was a case control study with 30 participants in each group. Young males between 18 and 35 years of age were included in the study. Participants in the cases group had AGA greater than stage 3. Blood pressure, anthropometry, fasting insulin and glucose levels in blood, lipid profile, total and free testosterone and TSH were investigated for all participants. Insulin resistance was calculated using HOMA-IR and metabolic syndrome criteria devised by National Cholesterol Education Program Adult Treatment Pannel III NCEP ATP III was used.

Results: Cases had a higher mean diastolic blood pressure and a more frequent family history of AGA than controls. Total and free testosterone levels were significantly more in participants with AGA than controls. There was no significant difference in Insulin resistance and Metabolic syndrome criteria between the cases and controls but the prevalence of Insulin resistance IR and metabolic syndrome MS increased with the severity of AGA.

Conclusion: In conclusion, more studies are required in order to objectively clarify whether early AGA can be attributed to dyslipidaemia due to androgens, IR alone, or MS due to IR. In the present study we could not establish a clear cut role of IR or MS, though the testosterones were significantly higher in the AGA participants suggesting the role of androgens.

Keywords: Androgenetic alopecia, Metabolic syndrome, Insulin resistance

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Introduction

Androgenetic alopecia AGA is a very common problem in men, starting at the age of early 20s and progressing gradually, becomes a great psychological burden for those affected. Genetics and hormones play a great role in AGA. Oestrogens, androgens, growth hormone, prolactin, thyroid hormones, Insulin Growth Factor-1 and fibroblast growth factor-7 are modulators of the pilous follicles and hair cycling[1]. AGA has a polygenic pattern and dihydrotestosterone binding to the androgenic receptor in the hair follicle of the scalp triggers genes accountable for progressive loss of thick pigmented terminal hair, a process called as miniaturization.

There have been many studies in the recent past, demonstrating an association with AGA and metabolic syndrome. Early onset of AGA has also been found to be related to insulin resistance in certain studies. Insulin resistance is a state in which a given concentration of insulin produces a less-than-expected biological effect. Obesity is the most common cause. This is followed by increased insulin secretion with compensatory hyperinsulinemia, to maintain normal glucose and lipid homeostasis[2]. Insulin has been suggested to play a role in the regulation of cutaneous androgen metabolism and hair-growth cycle[3]. But these results have not been duplicated in the various studies conducted. Because of the existing controversies in the relation between AGA and insulin resitance and metabolic syndrome, we undertook a study at our institution to find an association between the same in men with early onset of AGA.

Materials and Methods

This study was conducted on male subjects attending dermatology OPD of Bowring and Lady Curzon Hospital after obtaining signed Informed Consent. It was a case control study with 30 subjects in each group(Case-control ratio- 1:1). Our aim was (1) to contrast insulin resistance-related features in young male AGA cases and controls (2) to compare insulin resistance, using the homeostasis model assessment of insulin resistance (HOMA-IR) index, between cases and controls (3) to explore whether AGA is a clinical sign of insulin resistance or metabolic syndrome. Males between age 18 and 35 years of age, and with AGA of Hamilton Norwood stage≥3 was included in the cases group. The control group included men between 18 and 35 years of age, without AGA.

Females with AGA were excluded. Subjects with unsteady weight in the past 3 months, with other types of alopecia, acute or subacute concomitant illnesses, with glucose metabolic disorders, Coronary artery disease, coexisting endocrine disorders, hepatic or renal failure, on anti-obesity drugs , insulin sensitizing drugs/ insulin, androgens or anti-androgens, glucocorticoids within the previous 6 months were excluded from the study.

Complete clinical history, cardiovascular risk factors and family history was elucidated. Clinical anthropometry including weight, height, Body mass index (BMI), waist circumference and Blood pressure were measured in all subjects. The BMI was calculated by dividing body weight by the square of the height (kg/m2).Waist circumference was measured at the midpoint of the narrowest part between the bottom of the rib cage and the top of the iliac crest while the subject was standing erect, with the abdomen relaxed, arms at the sides and feet together, with weight equally divided over both legs. Blood levels of Glucose, insulin, total cholesterol, triglycerides, high density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol, free testosterone, total testosterone and thyroid stimulating hormones were estimated for all, after overnight fasting. The HOMA-IR index was calculated from the fasting concentrations of insulin and glucose using the following formula: HOMA-IR =fasting serum insulin (μU/ml) *fasting plasma glucose (mmol/ml)/22.5[3]. A normal HOMA-IR was set at ≤ 2.5. The presence of metabolicsyndrome was investigated in all cases according to criteria set by the National Cholesterol Education Program Adult Treatment Panel III (ATP III)[4].

All participants underwent digital photography and severity of alopecia was staged according to Hamilton Norwood scale. The protocol was approved by the Institute's Committee of Ethics and Research.

Statistical analyses:

The Student's *t*-test was used for intergroup comparisons of descriptive data (mean, standard deviation, frequency) in addition to comparisons of parameters. The chi-square test and Fisher's exact test were used for comparison of qualitative data. Spearman's rho correlation test was used for comparison of correlations between parameters. Statistical significance was attributed to two-tailed $p<0.05$.

Results

Sixty male subjects participated in the study, 30 cases and 30 controls. All were between 18 and 35 years of age. The mean age of men in cases and controls group was 25.37±4.6 and 22.73±3.08 respectively**(Table 1).** Family history of AGA was significantly more in the participants in cases group than the control group, with a p value of 0.0073**(Table 2).** Family history of hypertension, obesity and diabetes, was more in the cases group than controls, but there was no statistically significant difference. The groups were compared in terms of height, weight, waist circumference, BMI, systolic and diastolic blood pressure, total and free testosterone, total cholesterol, triglycerides, LDL, HDL and TSH. A statistically significant difference between average levels of SBP between the two groups was not observed. However, average levels of DBP were significantly higher in the AGA group compared with the controls(p=0.0442). The differences between the groups were found to be statistically meaningful (p > 0.05) with respect to free testosterone (p=0.0066) and total testosterone (p=0.0073) with the mean levels significantly more in cases compared to controls. All the other parameters were not statistically significant in the two groups. Total cholesterol and triglycerides were more in the cases, though not significantly different. The insulin level was 6.644±4.29 μIU/mL in the patient group and 8.27±4.65 μIU/mL in the control group, the difference between the two groups was not statistically meaningful (p > 0.05). The odds ratio (OR), using a HOMA-IR index ≥2.5, contrasting cases and controls, was 0.31 with 95 % confidence interval 0.08401 - 1.127, the p value being 0.1253 **(Table 3)**. Similarly the difference between the two groups with respect to fasting glucose and HOMA-IR was also not statistically significant. When the AGA patient group was classified according to the Hamilton-Norwood scale, 19 (63.33%) patients were of stage III, 7 (23.33%) of stage IV and 4 (13.33%) of stage V. When the stages were compared with regard to HOMA IR, the indices increased as the stage of alopecia increased**(Table 4).** When the groups were compared with respect to MS frequency, 10(33.33%) patients in the AGA group and 5(16.66%) participants in the control group were found to have MS, according to NCEP-ATPIII criteria. Though more in the cases, there was no statistically significant difference between the groups (p = 0.2326). There was also a linear relationship between number of cases with metabolic syndrome and stage of alopecia in the cases group. There was a significant correlation between HOMA IR levels and triglycerides in the cases group with a p value of 0.0186. Significant correlation was found between the stage of alopecia and systolic blood pressure, BMI, waist circumference and free testosterone levels **(Table 5).**

Table 1: Summary statistics table

	Cases		Controls		P value Unpaired t test	Remarks NS-Not significant
	Mean	SD	Mean	SD		
Anthropometry						
Age years	25.367	4.5900	22.733	3.0843	0.0229	Significant
BMI kg/m2	22.650	3.9549	22.962	3.5051	0.7469	NS
Waist circumference(cms)	86.467	10.9316	85.077	10.8652	0.6232	NS
Systolic mm/Hg	120.933	9.1687	118.400	8.0069	0.2590	NS
Diastolic mm/Hg	80.067	7.8342	75.867	7.9816	0.0442	Significant
Insulin Resistance						
Fasting glucose (mg/dl)	97.767	10.5689	98.000	11.1634	0.9340	NS
Fasting insulin(μU/ml)	6.643	4.2946	8.270	4.6509	0.1646	NS
HOMA IR	1.590	0.9910	2.016	1.2116	0.1414	NS
Hormones						
Total testosterone ng/dl)	649.195	230.0130	501.177	179.2639	0.0073	Significant
Free testerone pg/ml)	18.315	5.2045	13.836	6.8155	0.0066	Significant
TSH (μIU/ml)	2.191	0.9666	2.710	2.4361	0.2823	NS
Lipid profile						
Total cholesterol(mg/dl)	172.933	38.3944	160.833	34.8960	0.2066	NS
Triglycerides(mg/dl)	134.267	50.9360	113.300	56.4716	0.1365	NS
HDL(mg/dl)	39.567	8.6371	40.833	8.9330	0.5788	NS
LDL(mg/dl)	106.580	37.9213	95.913	28.9769	0.2258	NS

Table 2: Family History

Family history	Cases	%	Controls	%	P value		Odds Ratio	CI
AGA	17	56.67	6	20	0.0073	Significant	5.231	1.66-16.52
Obesity	8	26.67	3	10	0.1806	NS	3.273	0.7741-13.837
Diabetes	8	26.67	3	10	0.1806	NS	3.273	0.7741-13.837
Hypertension	8	26.67	6	20	0.7611	NS	1.455	0.4352-4.861

Table 3: Prevalence of IR and MS in cases and controls

	Cases	Controls	Odds ratio	P value
Metabolic syndrome	10(33.33%)	5(16.66%)	2.5	0.2326
HOMA-IR>2.5	4(13.33%)	10(33.33%)	0.31	0.1253
Both	3(10%)	2(11.11%)	1.556	1.000

Table 4: Prevalence of IR and MS with different stages of AGA

Grades	No. of cases	Percentage	HOMA IR>2.5	Mean HOMA IR	Metabolic syndrome
Stage 3	19	63.33	2 (10.53%)	1.382086	4(21.05%)
Stage 4	7	23.33	1 (14.29%)	4.714286	3(42.86%)
Stage 5	4	13.33	1(25%)	5.00000	3(75%)

Table 5: Correlation with stage of AGA

	Stage of AGA Correlation coefficient	p value	Remarks
Systolic BP	0.4939	0.0055	Significant
Diastolic BP	0.2228	0.2367	NS
Total cholesterol	0.3379	0.0678	NS
Triglycerides	0.1706	0.3673	NS
Fasting insulin	0.1516	0.4237	NS
Fasting glucose	0.1466	0.4396	NS
Free testosterone	-0.4211	0.0205	Significant
Total testosterone	-0.03537	0.8528	NS
BMI	0.3706	0.0438	Significant
Waist circumference	0.4938	0.0055	Significant

HOMA IR	0.1940	0.3043	NS

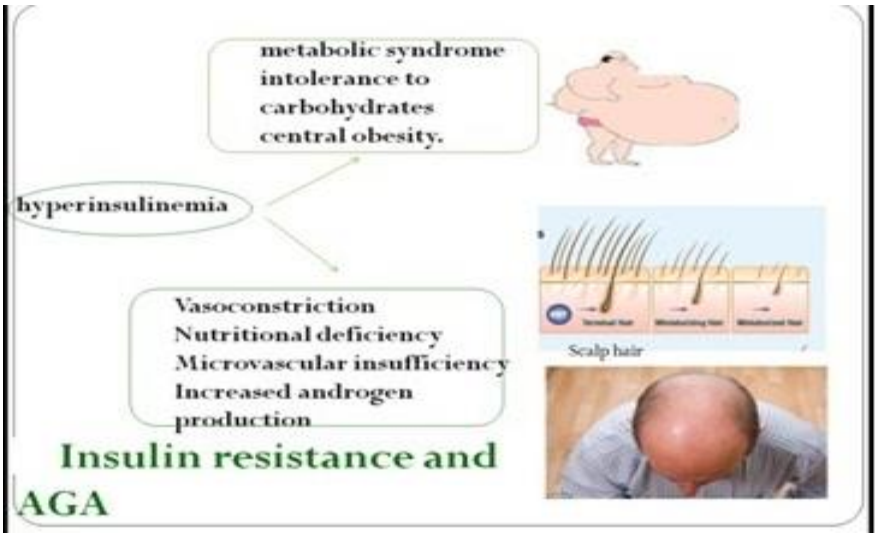

Fig. 1: Role of insulin in AGA

Discussion

The relationship between AGA and hyperinsulinaemia and cardiovascular related disorders was first suggested by Matilainen's group in their case–control study[5], but the mechanism of action has not been elucidated. Hyperinsulinemia caused by increased resistance to the peripheral action of insulin explains the association between androgenetic alopecia and cardiovascular disease. Elevated insulin levels are the main cause of metabolic syndrome and favor intolerance to carbohydrates and central obesity. Insulin has also been shown to favor vasoconstriction and nutritional deficiency in the follicles of the scalp, and it enhances the effect of DHT on follicular miniaturization[6,7]. **(Fig. 1).** In our study, Insulin resistance was calculated using HOMA IR index with a cut off of 2.5, and there was no significant difference found between the cases and controls unlike many studies in the past establishing a link between the two.

Dermal papilla is considered the main site of androgenic action, altering the production of soluble regulatory factors that influence the growth of hair follicle keratinocytes[8]. Systemically produced androgens also enter the hair follicle through passive diffusion[9]. The exact proportions of locally and systemically derived androgens present within the hair follicle are not known. Locally and systemically derived testosterone either directly binds to intracellular androgen or is metabolized into the more potent dihydrotestosterone (DHT), which, in turn, binds to androgen receptors with an approximate fivefold greater affinity. DHT is the key androgen required for the induction of AGA[10]. Despite the widely held belief that baldness is an indicator of increased male sexuality, there is little scientific evidence for this. In our study we found total and free testosterone levels significantly greater in the cases as compared to the controls. Similar results were found in a study conducted by Santiago etal[11] and Wahnfried et al[12.] High androgen levels contribute to the development of atherosclerosis and thrombosis, and increase the tendency to develop hypertension and hypercholesterolemia[13]. In the present study, average Diastolic BP was determined to be significantly higher in the AGA group. Two explanations[14] may be proposed for the association of hypertension and androgenetic alopecia: (1) androgens which bind to mineralocorticoid receptors might be responsible for the higher susceptibility to develop hypertension. (2) hyperaldosteronism which is considered to be responsible for most of primary hypertension may directly participate in the development of alopecia. However we did not investigate aldosterone levels in our study.

Dyslipidemia also occurs because of androgens or insulin resistance. In our study we found that total cholesterol and triglycerides were more in the cases though not significantly different from those of control group. These results were similar to the study conducted by Nabaie *et al*[15]. where they could not demonstrate a significant difference between AGA cases and control group with respect to levels of fasting insulin, glucose, HDL-cholesterol, and TG and insulin resistance.

In the present study there was no significant difference between the cases and controls with respect to metabolic syndrome criteria devised by NCEP ATP III. Metabolic syndrome comprises multiple features, including visceral obesity, hypertension, dyslipidemia, and impaired glucose tolerance. This constellation of conditions has also become synonymous with insulin resistance syndrome, which may be a more appropriate term, as insulin resistance is likely a primary link between the components of the metabolic

syndrome[16].But in our study we found that there was significant correlation only between insulin resistance and triglycerides. Insulin resistance and metabolic syndrome showed a significant correlation with the stage and severity of AGA in our study. Systolic blood pressure, BMI, waist circumference and free testosterone also showed significant correlation with the stage of alopecia.

Family history of AGA, diabetes, obesity and hypertension has been usually seen in patients with AGA in previous studies. In our study only family history of AGA was significantly more in patients with AGA than controls.

Limitations and Conclusions

To summarize, we found that total and free testosterone levels were higher in the AGA affected males, and Insulin resistance and metabolic syndrome increased in prevalence as the stage of alopecia increased, though there was no significant difference in the two groups for the same parameters. In our study we did not measure the blood levels of Sex hormone binding globulin SHBG, due to financial constraints; however the increased testosterone levels may be suggestive of low SHBG levels in patients with AGA. Since there is no concordance between the findings of this study and the previous studies which have also shown variable findings, more studies with larger sample size may establish a clear cut link between Insulin resistance, Metabolic syndrome and AGA.

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