CORONARY HEART DISEASE RISK FACTORS IN MALE-TYPE ANDROGENETIC ALOPECIA

Muhammad Asif Nawaz, Muhammad Qaiser Alam Khan*, Farooq Ahmad Khan***, Sameena Ghayur******

*Department of Pathology, Combined Military Hospital, Sialkot, **Combined Military Hospital, Bahawalpur, ****Department of Chemical Pathology & Endocrinology, Armed Forces Institute of Pathology, Rawalpindi, ****Department of Pathology, HIT Hospital Taxila

ABSTRACT

Introduction: Hyperandrogenaemia and androgenetic alopecia has some association with increased risk of coronary heart disease. Conflicting data has since been reported with regards to levels of biochemical markers of coronary heart disease risk factors in androgenetic alopecia.

Methods: A case control study was planned to evaluate biochemical markers of coronary heart disease in hyperandrogenaemia of males and androgenetic alopecia. Patients of androgenetic alopecia (n=22) were men with fronto-occipital baldness, aged 20-30 years.

Results: Healthy controls (n=20) were age-matched males without alopecia. The individuals with clinical evidence of any systemic or localised scalp disease were excluded. Levels of fibrinogen, glucose, Insulin, uric acid, total cholesterol, LDL-cholesterol and HDL-cholesterol were measured. The levels of total cholesterol, LDL-cholesterol, insulin, glucose, and uric acid in patients of androgenetic alopecia when compared with normal controls were raised significantly. Fibrinogen levels were raised while HDL-Cholesterol was lower in patients than controls but the difference was not significant statistically.

Conclusion: The results support the hypothesis that androgenetic alopecia in males is associated with increased risk of coronary heart disease.

Keywords: Alopecia, androgenetic, insulin, HDL-Cholesterol, LDL-Cholesterol, glucose, Uric acid, Fibrinogen,

INTRODUCTION

Androgenetic alopecia is the commonest cause of hair loss in males [1]. It is a common phenomenon affecting up to 50% of adult male population [2]. It usually starts in third decade of life but may commence soon after puberty [3]. Male pattern or fronto-occipital baldness is characterized by hair loss centered over the vertex with an m-shaped fronto-temporal recession. In females androgenetic alopecia usually assumes a diffuse pattern [4] but It occurs less often and starts a decade or so later than in males.

The classification system of male-pattern baldness was proposed on the basis of geographical areas of scalp involved and sequential pattern of alopecia observed in men [5]. It was modified by Norwood [6]. Later typical pattern found in females was described. In androgenetic alopecia progressive replacement of terminal hair by fine, virtually unpigmented vellus hair occurs with hair loss in distinct areas of the scalp [7]. No association has been found between bladness and dense hair pattern on the trunk and limbs [8]. Similarly no association has been established between hair loss and increased fertility [9].

The pathophysiology of androgenetic alopecia is not clearly understood. It occurs under the influence of androgenetic stimulation in individuals with genetic predisposition.

Correspondence: Chief Editor, Deputy Commandant Brig Farooq Ahmad Khan, Head of Chemical Pathology Department, AFIP, Rawalpindi.

The mode of inheritance cannot be established due to very high frequency of common baldness. It may have a multifactorial basis [10]. The development of baldness is associated with shortening of anagen (growth) phase of hair cycle and consequently with an increase in the proportion of telogen (resting phase) hair [11].

Various hormones including thyroid [12], cortisol [13] and sex hormones affect the growth of hair. Specifically, androgens are known to "up regulate" the pubic, axillary and beard hair receptors but "down regulate" genetically predisposed scalp hair in androgenetic alopecia. It has been reported that bald men have normal testosterone levels, tend to have lower sex hormone binding globulins (SHBG) and higher salivary testosterone, suggesting more bio-availability of androgens [14]. Elevated urinary [15] and sometimes serum dehydroepiandro-sterone (DHEA) levels have also been noted in male pattern baldness [16].

The metabolism of testosterone to 5-dihydrotestosterone (5 -DHT) is mandatory and the necessity of 5 ⇨-reductase is suggested by the evidence that bald male scalp has a greater capacity than non-bald scalp to convert testosterone to 5 □-DHT [17].

Lesko [18] showed that the risk of myocardial infarction increases with increasing extent of vertex baldness. The serum cholesterol levels of young bald males were shown to be higher than the age-matched non-bald

controls [19]. It has been suggested that insulin contributes to the hyperandrogenism by augmenting ovarian androgen production [20]. A population-based case-control study also proved that early onset of androgenetic alopecia is associated with severe coronary heart disease (CHD) [21].

The association of hyperandrogenaemia with biochemical risk factors of CHD e.g. fibrinogen, uric acid, LDL-cholesterol, HDL-cholesterol and hypertension is scarcely studied.

In our population no study has been reported regarding association of androgenetic alopecia with biochemical markers of Ischaemic Heart Disease. Therefore, a study was planned to evaluate the role of biochemical markers of Ischaemic Heart Disease in patients of androgenetic alopecia.

MATERIAL AND METHODS

The study was carried out in the department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology, Rawalpindi from December 1995 to December 1996.

Subjects:
Twenty-two young men (Group 1), aged 18-30 years, having various degrees of fronto-occipital male pattern baldness (Norwood type III vertex, IV through VII) were studied. Twenty subjects (Group 2) of almost same age and sex group, without any clinical evidence of common baldness were included as controls in the study. Only those subjects (bald/controls) were included in the study that had no other known local or any systemic disease including diabetes mellitus, hypothyroidism, hyperthyroidism, SLE or scleroderma.

Specimen Collection:
A total of 10 ml of venous blood was collected in the morning in fasting condition; 2 ml blood was immediately transferred to sugar bottle (containing sodium fluoride) and 2ml to containers with 4% potassium oxalate for fibrinogen estimation. Serum was obtained from the remaining blood and was sent to routine chemistry laboratory for estimation of lipid profile and uric acid.

The serum lipid profile, uric acid, plasma fibrinogen and plasma glucose estimation was done on the same day i.e. day of specimen collection. The Insulin assays were done in one batch after completion of specimen collection.

Methods:
Insulin levels were determined by radioimmunnoassay. The coat a count analyte procedure is a solid phase radioimmunoassay, where in ^{125}I labeled analyte competes for a fixed time with insulin in the patient sample for sites on analyte specific antibody. Because the antibody is immobilized to the wall of a polypropylene tube, simply decanting the supernatant suffices to terminate the competition and to isolate the antibody bound fraction of the radio labeled insulin. Counting the tube in gamma counter then yields a number, which converts by way of calibration curve to a measure of the analyte present in the patient sample.

The RIA controls were run at the same time and intra-assay CV was 4.9% for insulin.

Plasma glucose estimation was done by glucose oxidase method. Glucose is oxidized to D-gluconate by glucose oxidase with the formation of an equimolar amount of hydrogen peroxide. In the presence of peroxidase, 4-aminoantipyrine and p-hydroxybenzene sulfonate are oxidatively coupled by hydrogen peroxide to form a quinoneimine dye, intensely colored in red. The intensity of color in the reaction solution is proportional to the concentration of glucose in the sample.

Plasma fibrinogen was determined by using Biopool fibrinogen assay. This kit utilizes the clauss clotting time method for the determination of plasma fibrinogen levels, wherein excess bovine thrombin is used to clot diluted plasma. First, a standard curve is prepared using reference plasma of known fibrinogen content (Biopool NNCCP) at dilution of 1/5, 1/10, 1/20 and 1/40. When thrombin is added, the clotting time obtained is inversely proportional to the fibrinogen content. Next, patient plasma, at a dilution of 1/10, is clotted with thrombin and the resultant clotting time is used to interpolate fibrinogen level from the standard curve.

Serum uric acid estimation was done by enzymatic Trinder method, using kit by Lab Systems (Pvt. Ltd.). Uric acid in the sample is oxidised by uricase to allantoin. In this reaction 1 mole of hydrogen perioxide is formed for every mole of uric acid oxidized.

Hydrogen perioxide reacts with 2-hydroxy-3, 5-dichlorobenze sulfonic acid (DHSB) and 4-aminoantipyrine (4-APP) in a reaction catalyzed by horseradish peroxidase (HPOD), to give a quinoneimine dye. The intensity of the color of the solution of this dye is proportional to the concentration of uric acid in the sample.

This assay is carried out at 520 nm. The reaction is initiated by the addition of the sample to the reagent.

Total cholesterol, HDL-cholesterol and LDL-cholesterol estimations were done by CHOD-PAP, enzymatic calorimetric methods. In the presence of cholesterol

esterase, the cholesterol esters in the sample are hydrolysed to cholesterol and free fatty acids.

The cholesterol produced are oxidised by cholesterol oxidase to cholestenone and hydrogen peroxide. Hydrogen peroxide is detected by a chromogenic oxygen acceptor, phenol-ampyrone, in the presence of peroxidase. The red quinone formed is proportional to the amount of cholesterol present in the sample.

The enzymatic method is as accurate and precise as Abell-Kendall reference method. Within-run precision for total cholesterol assay was less than 4% (CV). The kits used were supplied by Mercks Diagnostics.

Serum triglycerides estimation was done by GPO-PAP method. In this procedure enzymatic hydrolysis of triglycerides occurs and subsequently liberated glycerol is determined by colorimetry.

Statistical Methods:
The data is presented as mean and SD. Data analysis for all analytes was done by using student's 't' test.

RESULTS

The serum levels of insulin in healthy controls were 21.5 (3.2-39.8) uIU/ml when compared with patients of androgenetic alopecia [37.7 (12.5-62.9) uIU/ml].

The levels in the patients were significantly higher than healthy subjects ($p < 0.05$). The plasma glucose level was also significantly high in bald men than in healthy controls [4.98 (4.57-5.39) and 4.58 (4.12-5.04) mmol/l respectively ($p < 0.01$)].

The plasma fibrinogen levels were 2.94 (2.44 -3.44) g/l in patients of androgenetic alopecia and 2.72 (2.30 - 3.14) g/l in healthy individuals. The difference was not statistically significant (p = NS).

Serum uric acid estimation showed significantly higher ($p < 0.01$) levels in bald men [303 (343 -263) umol/l] than in healthy controls [263 (216 -310) umol/l].

Serum total cholesterol in patients of androgenetic alopecia was significantly higher than healthy subjects Table 1). Serum HDL-cholesterol levels were lower in the patients of androgenetic alopecia than healthy subjects. However, the difference was not statistically significant (Table 1).

The ratio of total cholesterol to HDL-cholesterol in bald men was higher than healthy controls (Table 1). The serum levels of LDL-Cholesterol were also significantly higher in bald subjects than healthy controls (Table 1). The serum triglyceride level was relatively high in bald subjects but the difference from healthy controls was not significant (Table 1).

Table 1: Comparison of lipid profile of healthy and bald males. Results were compared using student's t- test.Parameters

Parameters	Healthy subjects (n=20) Mean ±SD	Androgenetic alopecia (n=22) Mean ±SD	*p value*
Total-cholesterol (mmol/l)	4.14 ± 0.51	4.55 ± 0.69	< 0.05
HDL-cholesterol (mmol/l)	1.015 ± 0.104	0.98 ± 0.074	NS
Total/HDL-cholesterol	3.89 ± 0.94	4.66 ± 0.7	< 0.05
LDL-cholesterol (mmol/l)	2.42 ± 0.36	2.84 ± 0.58	< 0.05
Triglycerides (mmol/l)	1.51 ± 0.78	1.89 ± 0.92	NS

DISCUSSION

The association of androgenicity with coronary heart disease and hypertension has been suggested [22]. The association of early onset androgenetic alopecia with coronary heart disease is also proved by a population-based case-control study [21]. The association of hyperinsulinaemia secondary to insulin resistance with hyperandrogenism has recently been suggested [23]. Several syndromes characterized by an elevated insulin level in association with hyperandrogenism have been described [23].

Our results showed significantly higher levels of insulin in patients of androgenetic alopecia than healthy controls. The individuals with known diabetes or with family history of diabetes mellitus were not included in the study. In the bald subjects, the significantly higher levels of insulin and glucose than healthy individuals indicate the possibility of insulin resistance. Experimental evidence suggested that insulin has actions that may promote atherosclerosis and hyperinsulinaemia with insulin resistance, increases the risk of CHD [24]. In another study fasting hyperinsulinaemia was shown as a good predictor of CHD [25]. It has been suggested that insulin plays some role in the regulation of serum SHBG and testosterone levels in normal weight and obese men [26]. Our study shows significantly higher levels of uric acid in bald subjects than the healthy controls. The role of uric acid in CHD and its association with hyperandrogenism has been seen in different studies. Lee [27] concluded that elevated serum uric acid may be involved in the obesity-insulin syndrome, which in turn may explain the relation of serum uric acid with coronary heart disease. In young women, serum uric acid concentration was found to be independently

correlated with free testosterone levels [22]. The role of fibrinogen and other coagulation factors in CHD have already been revealed by various studies [28]. Our data suggests higher fibrinogen levels in patients of androgenetic alopecia than normal subjects but the difference was not significant statistically. We did the fibrinogen estimation by utilising the clotting time methods which may have a lower sensitivity. It may be more appropriate to plan a future study utilising better quantitative method.

The speculation that male pattern baldness is a predictor of coronary heart disease is based on certain observations. Both baldness and CHD are more common in males than females, having more circulating androgen levels.

Similarly, at puberty serum HDL levels decrease as the circulating androgens levels are increased in males. Despite the identification of DHT receptors in heart [29]. The impact of DHT on myocardium, coronary vessels and atherosclerotic lesions is still not clear.

Our study of biochemical risk factors for CHD revealed significantly higher levels of total cholesterol and LDL-cholesterol in serum of bald subjects than healthy controls. Although decreased levels of HDL-cholesterol were also seen in the patients but the difference was not statistically significant.

Similarly the total cholesterol/HDL-cholesterol ratio was much higher in patients of androgenetic alopecia than healthy controls. Lesko [18] found in his study, a trend of increasing rate of myocardial infarction with increasing extent of vertex baldness in men under the age of 55 y.

Trevisan [19] found a significant interaction of elevated serum cholesterol level and fronto-occipital baldness which becomes weaker with increasing age. Future studies must clarify the issue with better quantification of baldness and its patterns, and simultaneous measurement of CHD risk factors. Till that, consideration of male-pattern baldness as a CHD risk factor remain speculative. It is more important to ascertain whether baldness itself is an independent risk factor of CHD.

CONCLUSION

Among biochemical markers of CHD, serum total cholesterol, LDL-cholesterol, insulin, uric acid and plasma glucose levels showed significant elevation in these patients of androgenetic alopecia. The elucidation of mechanisms by which increased serum androgen activity, either directly increasing the risk of CHD or potentiating the effects of other biochemical risk factors, need further work in the field.

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