ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

Cardiovascular Risk in Female Pattern Alopecia

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Manuscript Info

Manuscript History:

Received: 15 June 2015
Final Accepted: 15 July 2015
Published Online: August 2015

Key words: cardiovascular risk, female pattern alopecia

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Abstract

Loss of hair is a common complaint and may lead to psychosocial problems. Hair loss may be a benign and transient process, or can be a serious and permanent problem. The majority of hair loss complaints seen in both males and females are caused by androgen-dependent or increased telogen hair shedding. The aim of this study was to evaluate the serum lipid profile in females with FPHL and their possible effect on the development of CAD in a sub- set of Egyptian patients. Fifty four females were enrolled in the study; twenty seven female patients with FPHL and twenty seven normal female participants as control group. Results of this study confirm that there is a true association between the high serum lipid levels and the female AGA but the pathogenetic link is still not clarified. This true association based on the presence of significant high values of TC,TG and LDL-C in females with AGA compared to age matched healthy females.

INTRODUCTION

Loss of hair is a common complaint and may lead to psychosocial problems. Even the mildest forms of alopecia can cause considerable distress, and some degree of dysmorphophobia is experienced in a proportion of these patients. Hair loss may be a benign and transient process, or can be a serious and permanent problem. The majority of hair loss complaints seen in both males and females are caused by androgen-dependent or increased telogen hair shedding **(Agac et al., 2015)**.

Female pattern hair loss (FPHL) has emerged as the preferred term for androgenetic alopecia (AGA) in females owing to the uncertain relationship between androgens and this entity **(Olsen, 2001)**.

It is characterized by a reduction in hair density over the crown and frontal scalp with retention of the frontal hairline. In 1977, Ludwig clearly described the distinctive features of FPHL and classified it into three grades of severity referred to as Ludwig grades I, II, and III **(ludwig ,1977)**.

The Prevalence of AGA increase with advanced age, 12% of women develop FPHL by age of 29 years, 25% by age of 49 years, 41% by 69 years, and over 50% have some element of FPHL by 79 years **(Gan and Sindlair, 2005)**.

Correlation between (AGA) and life-threatening diseases, such as coronary artery disease (CAD) has been investigated. The association between male pattern baldness and CAD was first suggested by **Cotton et al. (1972)** but this association in women was not documented. Later on it was found that female AGA, like male patternn baldness, was associated with CAD in women younger than 55 years but the mechanism of this association was not clear **(Mansouri et al., 2005)**.

The effect of serum lipid parameters on atherosclerotic heart disease has been well documented. In particular, lipoprotein a (LP a) and apolipoproteins that have been shown as important independent risk factors for CAD **(Sathanur and Berenson, 1995 & Ari and Yigitoglu, 1997).**

An increased low density lipoproteins to high density lipoproteins (LDL:HDL) ratio has already been considered a sensitive predictor of cardiovascular risk **(Grundy and Zahed,1997).**

Few studies have focused on the effect of lipid parameters on the relationship between AGA and CAD **(Sasmaz et al.,1999 and Barud et al.,2002)**. Level of Lp(a) which is an important and genetically determined risk factor for CAD was found greater in some AGA patients than the critical level for atherosclerosis . So lipid profiles especially LP(a), should be measured in women with AGA to find out those at risk of CAD **(Agac et al., 2015)**.

Patients and Methods

This study was carried out in the out-patient Dermatology, Venerology and Andrology Clinics, Zagazig University Hospitals. Fifty four female were enrolled in the study, twenty seven female patients with female pattern hair loss by Ludwig grades and twenty seven normal female participants as control group. The study had the approval of the institutional review board (IRB) at Zagazig University. The subjects were divided into two groups (a, b). The demographic data of the two groups are demonstrated in table (1).

Participants were randomly divided into two groups:

The first group (case group): included 27 female patients aged 20 – 50 years having female pattern hair loss diagnosed clinically with Ludwig grades. According to ludwig classification 16 patients (59.3%) were ludwig grade 1, 10 patients (37.0%) were ludwig grade 2 and one patient (3.7%) was ludwig grade 3.

The second group (control group): included 27 healthy controls in the same age range.

A full history was taken including onset, course and duration of AGA symptoms suggestive of hyperandrogenism like (acne, hirsutism), and history of other system affection as cardiovascular (palpitation; dyspnea; chest pain….etc, hyper/hypothyroidism (weight gain or weight loss; hot or cold intolerance).

Dermatological examination was done to exclude signs of hyperandrogenisim as acne and hirsuitism. Local scalp examination for diagnosis of AGA that based on: clinical findings (the pattern of hair loss: reduction in hair density over the crown and widening of the central part**)** and family history of AGA. Patients were graded as stage I, II or III AGA according to clinical examination of pattern of hair loss that based on Ludwig's scale.

Investigations:

Patients and controls were subjected to the following After fasting of 8 hours, 5 ml of venous blood was drawn in a sterile syringe and submitted to the laboratory for centrifugation and isolation of blood serum and was kept at -20ºC until the test day.

The blood sample was used for lipid profile evaluation including cholesterol, triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL). They were measured by using Spin react kit (made in Spain).

Lipoprotein a was also measured by Enzyme Linked immunosorbent Assay (ELISA). Solid phase capture sandwich ELISA assay with a microwell format was used.

Results

The demographic data of the two groups are demonstrated in table (1).

Positive family history of cardiovascular disease in the case group was markedly higher compared with that of the control group, with a highly significant P value ($P<0.01$), table (2).

Lipid profile:

Total cholesterol (TC) in the case group ranged from 136 – 354mg/dl, with a mean of 238.7 ± 49.7mg/dl. While TC of the control group ranged from 160 – 225mg/dl with a mean of 192.9 ± 18.1mg/dl.

Triglycerides (TGs) level in the case group ranged from 112 – 296mg/dl, with a mean of 200.4 ±65.4mg/dl . Whereas, TG level in the control group ranged from 65 – 160mg/dl, with a mean of 98.7 ±22.3mg/dl.

Low density lipoprotein cholesterol (LDL-C) in the case group ranged from 69 – 255.8mg/dl, with a mean

of 155.2 ± 42.1mg/dl. On the other hand, LDL-C in the control group ranged from75.2 –154.5mg/dl, with a mean of 125.1 ± 20.8mg/dl.

High density lipoprotein cholesterol (HDL-C) in the case group ranged from 23.5 – 69.8mg/dl, with a mean of 43.1 ±10.5mg/dl . While HDL-C in the control group ranged from 33.1 – 52.7mg/dl, with a mean of 44.1 ± 5.8mg/dl.

Lipoprotein a (LP (a)) in the case group ranged from 10 – 81mg/dl, with a mean of 28.1 ± 16.5 mg/dl. While LP (a) in the control group ranged from 10 – 30 mg/dl ,with a mean of 9.6 ± 6.8 mg/dl. Patients had significantly high mean values of total cholesterol (TC), triglyceride (TG) level, and low density lipoprotein (LDL-C). HDL-C was found to be lower than in healthy controls despite that the mean value of HDL-C in both groups were within the normal range. LP (a) is higher in case group but statistically insignificant, table (3).

There was a statistically significant correlation between cholesterol level , LDL and lipoprotein a in patients of AGA and the severity of AGA according to Ludwig criteria as ($P < 0.05$) while the levels of HDL showed no significant correlation as ($P > 0.05$), table (4).

Ratio of TC: HDL-C in the case group ranged from 4.3 to 10, with mean of 6.7 ± 1.4 SD. On the othr hand, ratio of TC:HDL-C in the control group ranged from 1.9 to 7.6, with a mean of 4.5 ± 1.5 SD.

Furthermore, ratio of LDL-C: HDL-C in the case group ranged from 2.4 to 8, with mean of 4.9 ± 1.2 SD. While ratio of LDL-C:HDL-C in the control group ranged from 0.4 to 5.9, with mean of 3 ± 1.5 SD.

TC: HDL-C, and LDL-C:HDL-C in the case group were markedly higher compared with that of the control group, with a highly significant P value ($P<0.01$). table (5)

DISCUSSION

Androgenetic alopecia is the most common hair loss disorder, affecting both men and women. It leads to progressive miniaturization of the hair follicle with a usually characteristic pattern distribution in genetically predisposed men and women **(Blume-Peytavi et al., 2011)**.

Females have been found to have higher levels of 5-α reductase, more androgen receptors, and lower levels of cytochrome P450 (which converts testosterone to estrogen) **(Drake et al.,1996).**

Cardiovascular disease is the leading cause of death worldwide. Prevention and early detection of it, is the major goal of health care**(Günes et al., 2008)**. The main cause of heart disease and stroke is atherosclerosis which is a progressive disease characterized by the accumulation of lipids and fibrous elements in the large arteries. Furthermore, it is considered to be the underlying cause of approximately half of all deaths in westernized countries **(Lusis, 2000)**.

Sharrett et al. (1999) stated that high levels of (TGs) and low levels of (HDL-C) are associated with the transition from atheroma to atherothrombosis.

Dyslipidemia has been studied as a valuable predictor of cardiovascular disease. For instance, increased LDL-c/HDL-c ratio has already been considered a sensitive predictor for CHD in men, and TC/HDL-C ratio has been found to be an even better predictive metabolic index for CHD risk in a large study **(Lemieux et al.,2001)**.

Furthermore, LP (a) has been shown as an important independent risk factor for CAD in many studies. Measurement of the LP (a) level has been recommended to determine the risk of myocardial infarction **(Sathanur and Berenson, 1995 & Ari and Yigitoglu ,1997)**.

Increased level of serum LP(a) is said to be associated with endothelial dysfunction and CAD as it has a structure similar to LDL but is attached to a glycoprotein called apolipoprotein- a. It has sticky adhesive nature and can easily attach to LDL, calcium, and other components in an atherosclerotic plaque on the blood vessel wall. Moreover, due to its similarity with plasminogen, it competes with plasminogen for the binding with fibrin inhibiting its breakdown thus promotes blood clot formation. It also activates immune cells including monocytes and macrophages which help in inducing inflammation. These effects altogether help in inducing plaque formation and promote clot formation after the plaque is ruptured **(Kamstrup et al.,2009**).

The pathogenetic mechanisms of atherosclerosis are quite well known, however the pathogenetic link between alopecia and atherosclerosis is not clear yet **(Arias-Santiago et al., 2009)**. Pathogenic mechanism explaining the increase in cardiovascular risk in AGA patients may be attributed to the greater peripheral sensitivity

of the receptors to androgens produced in AGA patients. The free testosterone is transformed by action of 5α-reductase into DHT. As the 5α-reductase and DHT receptors are present in blood vessels and heart as well as the hair follicles, this increased sensitivity leads eventually to follicular miniaturization at the follicular level and proliferation of vessel smooth-muscle cells, a key phenomenon in atherosclerosis alongside lipid deposits, at the vascular level **(Arias-Santiago et al., 2010)**.

Cotton et al. (1972) was the first one to show an association between the occurrence of coronary artery disease and baldness, therefore he suggested that male androgenetic alopecia (MAGA) could be a risk factor for cardiovascular disease. However, few later studies have analyzed the relationship between AGA in women and cardiovascular disease and supported the hypothesis that AGA mainly in women < 55 years is associated with coronary artery disease **(Matilainen et al., 2003 and Mansouri et al., 2005)**.

Thus the objective of this study was to evaluate lipid levels in women with AGA and in healthy controls to evaluate the possibility of cardiovascular risk factors in females with AGA.

There was a high statistically significant positive family history of cardiovascular disease in patients of the current study compared to healthy controls. On the contrary, **Arias-Santiago et al. (2010)** found no significant differences between women with AGA and women without AGA as regard family history of cardiovascular disease.

Regarding lipid parameters, Female patients with AGA showed marked dyslipidemia when compared to healthy controls as they had significantly higher mean values of (TC) , (TG) , (LDL-C) ,TC:HDL-Cand LDL-C:HDL-C.

This was in agreement with the study done by **(Arias-Santiago et al., 2010 d)** who reported that women with AGA have higher significant mean values than non-alopecic women for TC (196.1 ± 33.6) P value (0,01) ,TG (123.8± 82.4), P value (0.00) LDL-C (114.1± 27.3) P value (0.00) , and LDL-C:HDL-C (2.1± 1)P value (0.00) and lower significant HDL-C (56.8 ± 14.7) P value (0.00) than healthy controls. However, as regard HDL-C, the present study showd low but insignificant decrease of mean value of HDL-C (43.1 ± 10.5) P value(0.65) in patients versus controls.

Trevisan et al. (1993) showed that patients with fronto-occipital baldness had higher serum cholesterol and blood pressure on the average compared to participants of similar age with no baldness. (**Sharma et al., 2013)** showed that the TG (166,79± 57.94) P value(<0.0001) and LDL (70.38± 16.34) P value (< 0.0001) levels in patients with AGA were significantly higher than controls as in our study.

On the other hand, **Matilainen et al. (2003)** could not report any significant differences in lipid profiles at all between women with AGA and women without AGA. This may be due to the fact that they didn't exclude patients receiving hypocholesterolemics drugs as we did.

As regard to the LP(a) level, our patients showed high level of LP (a) but insignificant incomparison to the controls (28.1 ± 16.5) P value (0.07), although previous studies showed that LP(a) levels in patients with AGA was significantly higher than in controls **(Agac et al., 2015 & Sharma et al.,2013 and Mosbeh et al., 2014)**. The values were (26.01 ± 29.50) P value(0,002) , (47.10 ± 52.54) P value (0,001) , (27.37±6.117) P value(<0.00001) (48.10 ± 52.53) P value (0,001)respectivly .That may be due to larger sample size in their studies,so further studies should be done on larger number of GA patients to confirm the correlation.

In this study,there was significant correlation between lipid parameters and Ludwig stage of AGA, and this is in contrary with the study done by **Arias-Santiago et al., (2010)** who reported that no significant differences were observed between Ludwig degree of AGA and lipid parameters. However, other studies done on MAGA showed that there was a correlation between the pattern of AGA and lipid parameters (**Lesko et al 1993 and Rebora, 2001)**.

Finally, lipid values may be regarded as a risk factor for cardiovascular disease and AGA could be considered an alarming sign for cardiovascular diseases. The unfavorable lipid profile in men and women with AGA could explain its association with CHD.

Conclusion

Results of this study confirm that there is a true association between the high serum lipid levels and the female AGA but the pathogenetic link is still not clarified. This true association based on the presence of significant high values of TC,TG and LDL-C in females with AGA compared to age matched healthy females.

Females with AGA could carry risk factor of cardiovascular disease due to their high risk of atherosclerosis more than healthy females as appeared from measurement of ratio of TC:HDL-C and LDL-C:HDL-C.

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Table (1): The socio-demographic characteristics of the studied groups

	Patients N = 27	**Controls N = 27**	**t**	**P**
Age (years)				
Range	(23 – 48)	(21 – 43)	3.2	0.17
Mean ± SD	(37.1 ± 7.9)	(34.7 ± 5.7)		N.S

P = level of significance

P value is significant < 0.05

N.S (non significant)

Table (2): The family history of some diseases among the studied groups

	Patients	**Controls**	**t**	**P**
	N = 27	**N = 27**		
	No (%)	**No (%)**		
AGA	21 (77.8 %)	2 (7.4 %)	24.7	0.00** H.S
CVS	15 (55.6 %)	1 (3.7 %)	16	0.00** H.S

** **p** value is highly significant (H.S) <0.01

Table (3):Values of the lipid parameters in Patients and control groups

Lipid level (mg/dl)	Patients N = 27	Controls (N = 27)	t	P
TC	(238.7 ± 49.7) (136 – 354)	(192.9 ± 18.1) (160 – 225)	4.51	0.00** H.S
TGs	(200.4 ± 65.4) (112 – 296)	(98.7 ± 22.3) (65 – 160)	7.64	0.00** H.S
LDL-C	(155.2 ± 42.1) (69 – 255.8)	(125.1 ± 20.8) (75.2 – 154.5)	3.39	0.00** H.S
HDL-C	(43.1 ± 10.5) (23.5 – 69.8)	(44.1 ± 5.8) (33.1 – 52.7)	- 0.46	0.65 N.S
LP (a)	(28.1 ± 16.5) (10 – 81)	(19.6 ± 68) (10 – 30)	2.4	0.07 N.S

** **p** value is highly significant (H.S) <0.01

N.S (non significant)

Table (4): Correlation between AGA severity (Ludwig criteria) and lipid profile in patients:

Variable	Ludwig criteria	
	R	**P**
Cholesterol	0.33	0.03*
HDL	- 0.23	0.06

LDL	0.52	0.02*
Lipoprotein (a)	0.28	0.04*

* **P** value is significant < 0.05

Table (5): Comparison between TC: HDL-C, LDL-C: HDL-C in Patients and controls

	Patients N = 27	**Controls (N = 27)**	**T**	**P**
TC: HDL-C	(6.7 ± 1.4) (4.3 – 10)	(4.5 ± 1.5) (1.9 – 7.6)	7.64	0.00**
LDL-C: HDL-C	(4.9 ± 1.2) (2.4 – 8)	(3 ± 1.5) (0.4 – 5.9)	4.51	0.00**

** **p** value is highly significant (H.S) <0.01