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ORIGINAL CONTRIBUTION

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Metabolic syndrome in androgenetic alopecia patients; Is serum regulated on activation, normal T-cell expressed and secreted the missing link?

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Abstract

Background: Androgenetic alopecia (AGA) is the most common cause of hair loss affecting both men and women. There are many conflicting results about the relationship between AGA and metabolic syndrome, (MetS) and the pathogenesis of the metabolic disorders in AGA patients is not completely elucidated.

Aims: Evaluation of the prevalence of MetS and the possible role of RANTES in pathogenesis of the MS among AGA patients.

Methods: A total of 160 subjects were enrolled in this work; included 100 patients clinically diagnosed with AGA and 60 apparently healthy control subjects. They were evaluated for MS components according to National Cholesterol Education Program (NCEP) adult treatment panel 3 (ATP3) and measurement of serum RANTES level using ELISA kits.

Results: Metabolic syndrome was present in 30.0% of AGA patients and in 10.0% of the control group ($P = .038$), Studied AGA patients showed significantly higher serum RANTES when compared to control group (P value $< .001$). Moreover, serum RANTES levels were significantly positively correlated with BMI, FBG, TC, and LDL-c levels in AGA patients with MetS.

Conclusion: Metabolic syndrome components were prevalent among AGA patients. Serum RANTES level was significantly higher in all AGA patients and specifically in those with MS as it was significantly positively correlated with some MetS components which reflects its possible role in pathogenesis of MetS in AGA patients.

KEYWORDS

androgenetic alopecia, metabolic syndrome, RANTES

1 | INTRODUCTION

Androgenetic alopecia (AGA) is the most common cause of hair loss. In men, up to 30% over the age of 30 and more than 50% over the age of 50 are affected.[1] There are several studies investigating the association between metabolic syndrome (MetS) and AGA. MetS is a group of metabolic disorders including; glucose intolerance, insulin resistance (IR), central obesity, dyslipidemia, and hypertension associated with increased risk of cardiovascular disease.[2] Early screening of MetS and its components is beneficial in patients with AGA.[3]

Regulated on activation, normal T-cell expressed and secreted (RANTES) belongs to the family of CC chemokines that recruits and activates various subtypes of cells as T cells, monocytes, basophils, eosinophils, or mast cells. It is expressed by adipocytes and has been

hypothesized to mediate leukocyte infiltration of adipose tissue in obesity.[4] Also, it has shown that it contributes to different pathologic processes including; cancer, allergy, infection, and atherosclerosis [5] and it was suggested that RANTES acts as a biomarker of MS, as being a potent proinflammatory factor.[6]

The systemic inflammation in AGA has not been extensively studied, but it raises the possibility of identifying new cardiovascular risk factors among patients with AGA. Therefore, we tried to investigate the prevalence of MetS among AGA patients and the possible role of RANTES in the pathogenesis of metabolic disorders in AGA patients.

2 | SUBJECTS AND METHODS

2.1 | Study Population

A total of 160 subjects were enrolled in this work; 100 patients clinically diagnosed with AGA and 60 apparently healthy control subjects. Patients were excluded if they are less than 18 years; complaining of other types of alopecia, and other skin diseases associated with MS as psoriasis, patients with thyroid diseases, familial hyperlipidemia, nephritic syndrome, chronic renal failure, and patients on drugs that are known to cause hyperglycemia, hyperlipidemia, or hypertension.

Patients were diagnosed with AGA based on clinical findings, pattern of increased hair thinning on frontal/vertex scalp with higher hair density on occipital scalp zone, and they were graded according to the Hamilton-Norwood classification system [7] for men and the Ludwig grading system for women.[8]

2.2 | Compliance with Ethics Guidelines

The study was approved by the local ethics committee on research involving human subjects in the faculty of Medicine; University in agreement with the Declaration of Helsinki. An informed consent was obtained from each subject prior to participation.

2.3 | Data Collection and procedures

Biometric data such as weight, height, and waist circumference were recorded. To determine waist circumference, a nonextendable measuring tape was placed at the level of the umbilicus. Body Mass Index (BMI) was calculated by weight in kilograms/ Height in meters 2 (Quetelet's Index). Metabolic Syndrome was defined according to the National Cholesterol Education Program (NCEP) adult treatment panel 3 (ATP3) by the presence of 3 of the following criteria;

- Abdominal circumference greater than 102 cm in men and 88 cm in women.
- Hypertriglyceridemia > 150 mg/dL.
- High density lipoprotein cholesterol (HDL-C) less than 40mg/dl in men and less than 50 mg/dL in women.
- Blood pressure >130/85 mm Hg.
- Glycemia >100 mg/dL.
- A BMI_>_25 was taken as overweight and BMI greater than or equal to 30 as obesity, as per WHO definition.

2.4 | Laboratory Tests

Three ml venous blood was collected from each subject by clean venipuncture using disposable plastic syringe twice; the first sample after 6-8 hours fasting (for RANTES and FBS) and the second sample after 12-14 hours of fasting (for lipid profile). Samples placed on a plain tube (without anticoagulant) for serum separation. The tube was left at room temperature for 30 minutes till coagulation and then was centrifuged (at 1500 rpm for 15 minutes). The resultant serum was tested for FBS and lipid profile, and the rest from first sample stored at −20°C for further RANTES testing. A double-antibody sandwich enzyme-linked immunesorbent assay (ELISA) was used to detect serum level of RANTES using a commercial Human RANTES ELISA Kit for research use only (Cat #: 201-12-0085, SunRedBio, China).

2.5 | Statistical Analysis

Data were collected, revised, coded, and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations, and ranges when their distribution found parametric while nonparametric data were presented as median with interquartile ranges. Also, qualitative variables were presented as number and percentages. The comparison between groups with qualitative data was done by using chi-square test and Fisher's exact test when the expected count in any cell found less than 5. The comparison between two groups with quantitative data and parametric distribution was done by using independent t test while nonparametric data were compared using Mann-Whitney test. Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group. Receiver operating characteristic curve (ROC) was used to assess the best cutoff point of serum RANTES between AGA patients with and without MS with sensitivity, specificity, positive predictive value, and negative predictive value. The confidence interval was set to 95%, and the margin of error accepted was set to 5%. The *P* value was considered significant if <.05.

3 | RESULTS

Studied patients and healthy controls were age- and sex-matched. AGA patients showed significantly higher WC, BMI, FBG, TG, and LDL-C (*P* value <.001, <.001, .030, .016, and <.033, respectively)

than healthy controls. RANTES serum levels were also significantly higher in AGA than control (*P* value <.001) (Table 1).

Metabolic syndrome defining criteria were present in 30.0% of AGA patients and in 10.0% of the control group (*P* = .038). Serum RANTES level was significantly higher in AGA patients with MetS than those without (Table 2). Moreover, it was significantly positively correlated with BMI, FBG, TC, and LDL-C levels in AGA patients with MetS (*P* < .05 each) (Figures 1, 2, 3, and 4). Receiver operating characteristic curve (ROC) was used to determine sensitivity and specificity of serum level of RANTES in early diagnosis of MetS among AGA patients when cutoff point > 495.8 ng/L with sensitivity and specificity 100% (Figure 5).

4 | DISCUSSION

Several studies investigated the association between AGA and metabolic MetS revealed conflicting results.[9-20] The metabolic syndrome is a group of disorders associated with increased risk of CVD.[17] Different factors such as genetic predisposition, IR, obesity, hypertension, dyslipidemia, vascular abnormalities, inflammation, hyperandrogenism, uric acid deficiency, and vitamin D deficiency are involved in the pathogenesis of MetS.[9]

Although a relation has been reported between these two disorders, the pathophysiological link between them is not fully understood.[2] However, two theories have been proposed; excess of androgens in both of AGA and CVD and hormonal changes as hyperandrogenism may play a role in the development of AGA and hypertension.[18]

In the current study, MetS components were significantly present in 30.0% of studied AGA patients and in 10.0% of the control group (*P* = .038). This was consistent with the results of other previous studies.[9-16] However, Gok et al[2] and Nabaie et al[19] did not find a relationship between AGA and MetS defining parameters. These different results and the significant association between AGA, IR, and MetS reported in the previous studies could be explained by the presence of other confounding factors as advanced patients' age and so metabolic disorders could be reasonable.

Also Giltay et al[20] in their study, including 81 female-to-male transsexuals treated with testosterone esters had male-pattern baldness did not reveal any CVD risk factors such as hypertension, dyslipidemia, or IR among studied patients.

Our results revealed that mean serum level of RANTES was significantly higher in AGA patients than healthy controls, which may be attributed to the proinflammatory role of RANTES.[4] Several literature reports that can link AGA to increased oxidative stress

TABLE 1 Baseline data in the studied groups

Baseline data		Patients group No. = 100	Control group No. =60	*P* value
Age (years)	Mean ± SD	33.82 ± 6.6	31.1 ± 7.1	.085
Sex				
Female	N (%)	40 (40.0%)	24 (40.0%)	1.000
Male	N (%)	60 (60.0%)	36(60.0%)	
BMI (kg/m^2)	Mean ± SD	26.1 ± 2.46	24.8 ± 1	**<.001***
Waist circumference (cm)	Mean ± SD	84.7 ± 10.4	75.8 ± 5.3	**<.001***
SBP (mm Hg)	Mean ± SD	126.6 ± 15.6	120 ± 13.4	**.057***
DBP (mm Hg)	Mean ± SD	87.40 ± 9.4	80.33 ± 7.6	**<.001***
FBG (mg/dL)	Mean ± SD	95.3 ± 23.1	85.5 ± 10	**.030***
Total cholesterol (mg/dL)	Mean ± SD	188.7 ± 41.9	172.6 ± 38.6	.091
TGs (mg/dL)	Mean ± SD	125.3 ± 32.4	107.2 ± 30.9	**.016***
HDL-c (mg/dl)	Mean ± SD	44.2 ± 3.2	46.3 ± 3.1	.147
LDL-c (mg/dL)	Mean ± SD	123.9 ± 32.9	103.5 ± 31.7	**.033***
Serum RANTES (ng/L)	Mean ± SD	904.5 ± 301.4	352.1 ± 87.9	**<.001***
	Range	618.2 - 1978.2	140.1 - 495.8	
Met S				
No MetS	N (%)	70(70.0%)	54(90.0%)	**.038***
MetS	N (%)	30(30.0%)	6(10.0%)	

Bold entries indicate significant values.

Abbreviations: N, number; SD, standard deviation.

*Indicates significant values.

TABLE 2 Comparison between AGA patients with and those without Met S

			Without Met S N = 70	With Met S N = 30	*P* value
Age (yrs)		Mean ± SD	35.2 ± 7.6	39.2 ± 8.3	.106
Sex	Female	N (%)	46 (65.7%)	14(46.7%)	.208
	Male	N (%)	24(34.3%)	16(53.3%)	
Duration of AGA (years)		Mean ± SD	9.6 ± 3.1	10.5 ± 3.2	.557
Grading N; N (%) (Total = 60 male patients)	II	N (%)	8 (11.4%)	0	.158
	III	N (%)	18 (25.7%)	12 (40%)	
	IV	N (%)	14 (20%)	0	
	V	N (%)	2 (2.9%)	0	
	VI	N (%)	2(2.9%)	2 (6.7%)	
Grading L; N (%) (Total = 40 female patients)	I	N (%)	10 (14.3%)	2 (6.7%)	.056
	II	N (%)	16(22.9%)	8 (26.7%)	
	III	N (%)	0	6 (20%)	
Serum RANTES (ng/L)		Mean ± SD	822.3 ± 240.7	1096.2 ± 305.7	.005*
		Range	618.2 ± 1722.2	637.7 ± 1978.2	

Abbreviations: N, number; SD, standard deviation.

*Indicates significant values.

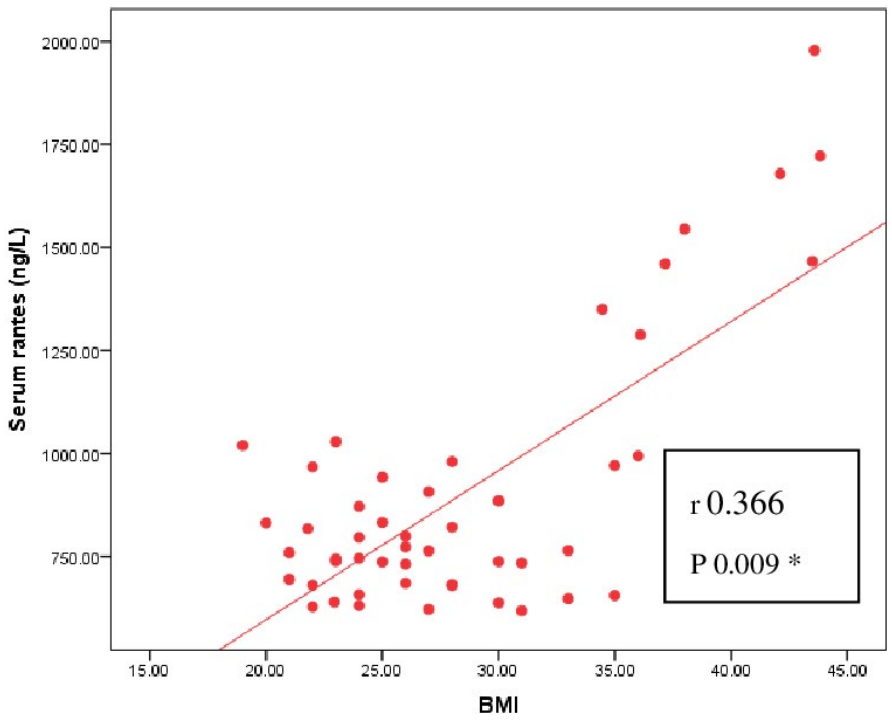

FIGURE 1 Significant positive correlation between serum RANTES level and BMI in AGA patients

revealed that AGA was associated with increased risk factors for cardiovascular disease and with increased presence of inflammation..[15,21-23] In addition, cytokines, chemokines, and some chemokine receptors including RANTES have been found to be upregulated by oxygen radicals.[24]

In addition, serum levels of RANTES in AGA patients were positively correlated with MS components; FBG, serum TC, and LDL-c levels supporting the previous findings about RANTES involvement in adipose macrophage infiltration and IR pathogenesis as it causes chemotaxis of mononuclear cells.[5] Also, enhanced RANTES expression in peripheral blood mononuclear cells from patients with familial hypercholesterolemia has been reported by Holven et al.[25] Moreover, it was reported that elevated circulating RANTES levels may result in reduction of glucose-dependent secretion of glucagon-like peptides 1 and 2 and impairment of glucose-induced insulin secretion.[26]

Circulating RANTES significantly correlated with waist circumference and BMI. This was in agreement with Huber et al[27]; who

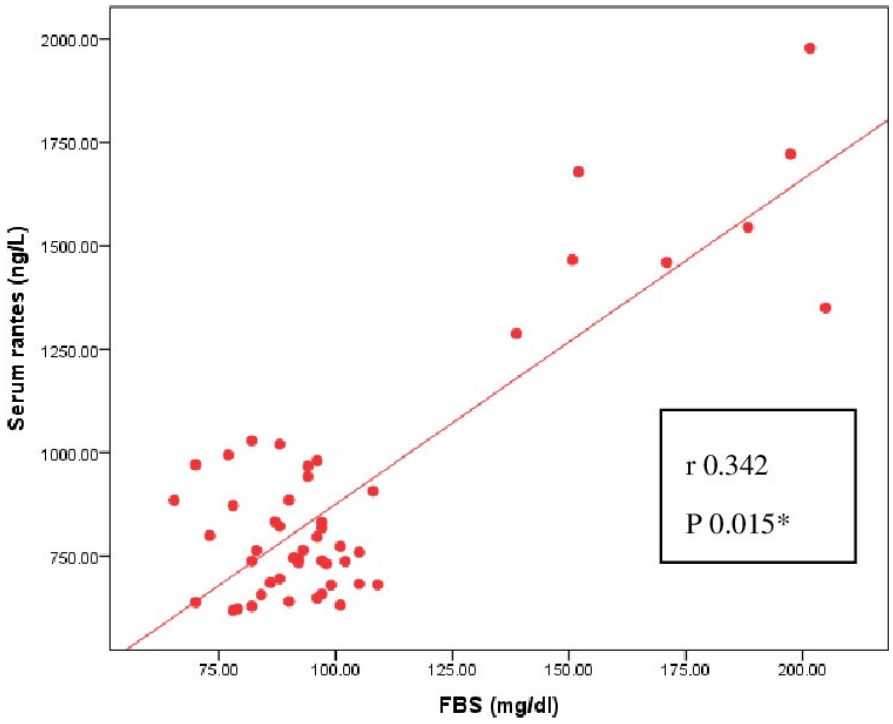

FIGURE 2 Significant positive correlation between serum RANTES level and FBG level in AGA patients

demonstrated that serum concentrations of RANTES were significantly elevated in obese versus lean subjects.On the contrary, Dworacka et al[28]found that circulating RANTES weakly correlated with WC and did not correlate with BMI.

It was demonstrated that inflammation during type 2 diabetes course is related to hyperlipidemia[29] and as it has been reported that hyperglycemia might be a reason for increased serum RANTES levels[30] we focused our attention on the associations between essential hallmarks of diabetes; carbohydrate and lipid metabolism disturbances and circulating RANTES. Intriguing correlations were revealed in the current work results between this chemokine and fasting glycaemia (r 0.342, p 0.015), and this correlation was especially interesting with respect to the results presented by Dworacka et al[28] and Holmer-Jensen et al,[31] who reported that circulating concentrations of RANTES are greatly affected in the postprandial period.

We found that RANTES levels were significantly positively correlated with hypercholesterolemia, this was similar to previous results of Feng et al.[32] Also, this was in line with other studies reporting significantly elevated circulating RANTES levels in patients with dyslipidemia[33] and MetS.[6] Moreover, our results suggest that serum level of RANTES could be used as a biomarker in early diagnosis of

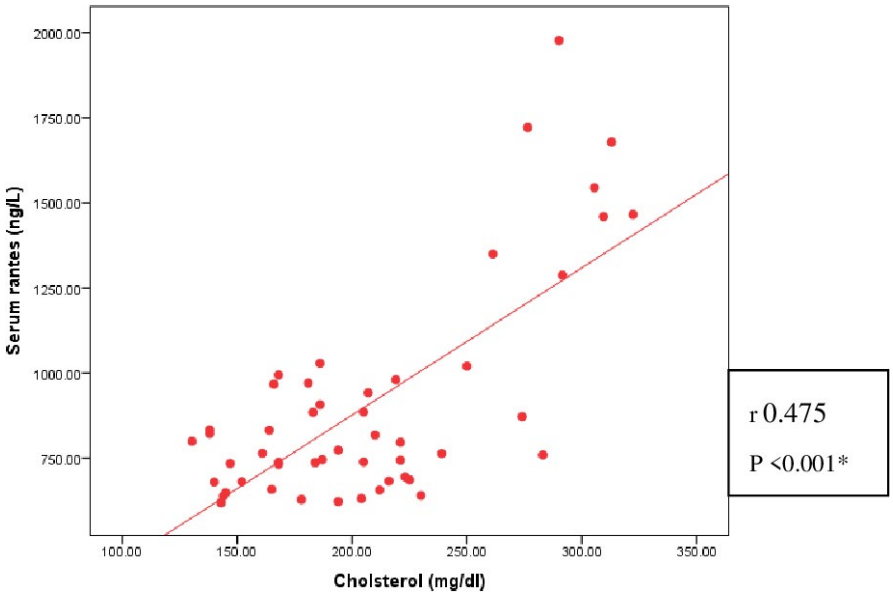

FIGURE 3 Significant positive correlation between serum RANTES level and serum total cholesterol (TC) level in AGA patients

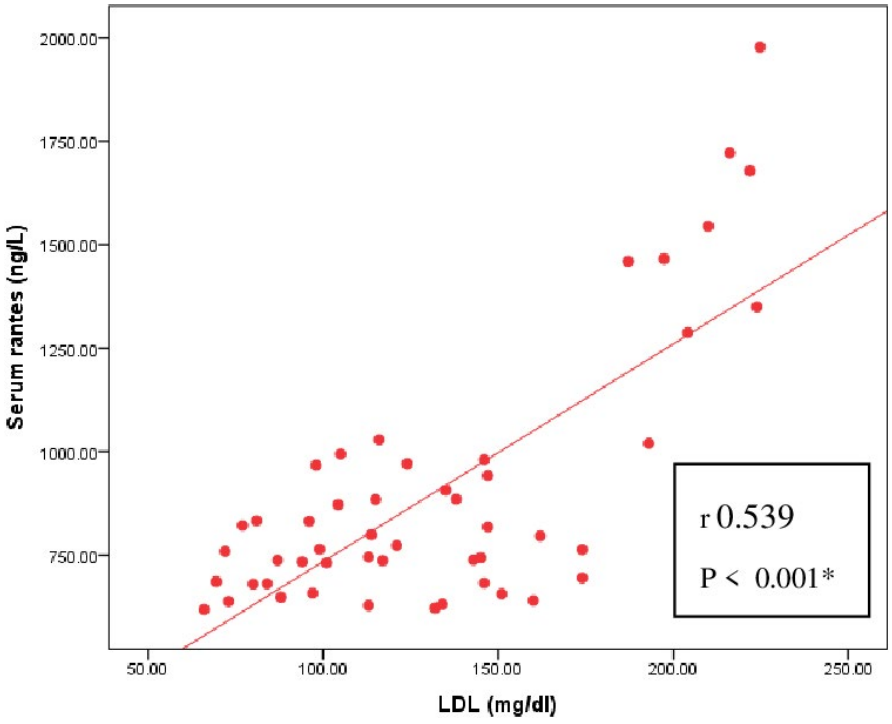

FIGURE 4 Significant positive correlation between serum RANTES level and serum LDL-C level in AGA patients

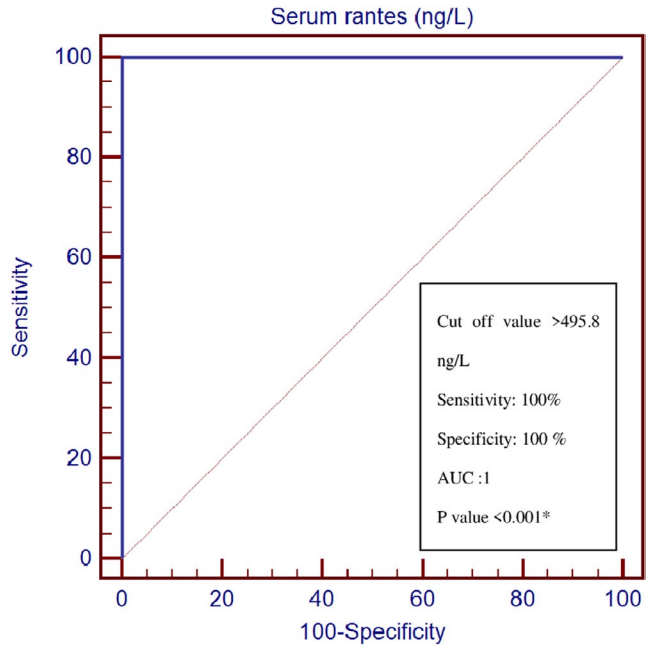

FIGURE 5 ROC analysis of serum RANTES level sensitivity and specificity in early diagnosis of MS among AGA patients

MetS among AGA patients when cutoff point > 495.8 ng/L with sensitivity and specificity 100%

5 | LIMITATIONS

The limitations of the study were small sample size and lack of measurement of insulin level.

6 | CONCLUSIONS

Metabolic syndrome components were more prevalent among AGA patients than healthy controls. Our study results suggest that RANTES might be not only the forerunner of metabolic components among studied AGA patients but also, it could be used as a reliable biomarker with high sensitivity and specificity in early prediction of the MetS. However, further larger scale studies are required to clarify the precise mechanisms by which RANTES predispose to MetS in AGA patients.

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CONFLICT OF INTEREST

The authors have declared no conflicting interests.

AUTHOR CONTRIBUTIONS

Mustafa AI MD, El-Habbak DM MD, and Abdel Halim W MD performed the research. Mustafa AI MD designed the research study. Abdel Halim W MD contributed essential reagents or tools. Fawzy E phD analyzed the data. Mustafa AI MD, El-Habbak DM MD, and Fawzy E phD wrote the paper.

COMPLIANCE WITH ETHICS GUIDELINES

The study was approved by the local ethics committee on research involving human subjects in the faculty of Medicine; Benha University in agreement with the Declaration of Helsinki. An informed consent was obtained from each subject prior to participation.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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