ORIGINAL ARTICLE

Role of Serum Ghrelin and Ghrelin Gene Polymorphism (rs34911341) in Psoriatic Arthritis

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ABSTRACT

Background: *The novel ghrelin hormone plays a crucial role in many inflammatory diseases. Also, the ghrelin gene has been associated with the susceptibility of several autoimmune disorders.* ***Objective:*** *This research aimed to study the role of ghrelin level in psoriatic arthritis (PsA) and to assess the association of ghrelin gene polymorphism rs34911341 with the susceptibility to PsA.* ***Methodology:*** *A case-control study was conducted on 63 PsA patients and 63 healthy controls. Patients were assessed for PsA activity, serum ghrelin was measured by ELISA, and the ghrelin gene single nucleotide polymorphism (SNP) rs34911341 was detected by polymerase chain reaction and restriction fragment length polymorphism analysis.* ***Results:*** *A significant higher level of ghrelin ($P<0.001$) was found among the case group. There was a significant negative correlation between ghrelin level and DAPSA ($r=-0.697$, $P<0.001$). ROC curve analysis of ghrelin performance showed that at a cut-off value of ≥30.4, serum ghrelin was 82.8% sensitive and 94.1% specific for detection of low PsA activity. No significant difference was found between the groups regarding the ghrelin gene SNP rs34911341 ($P>0.05$). The ghrelin gene was not related to the PsA disease activity. However, the gene SNP rs34911341 was significantly related to both BMI ($P=0.028$) and triglyceride levels ($P=0.005$).* ***Conclusion:*** *The ghrelin hormone has a significant role in PsA and could be a biomarker for predicting low disease activity. Ghrelin gene polymorphism SNP rs34911341 has no association with PsA; however, it could be associated with obesity and metabolic changes in PsA.*

INTRODUCTION

Psoriasis is a chronic autoimmune illness that affects 0.33%-0.6% of people in many racial groups[1, 2]. Chronic inflammation caused by proinflammatory cytokines results in peripheral insulin resistance and atherogenesis[3]. Consequently, this causes hypertension and type II diabetes mellitus (DM), the conditions that are implicated in metabolic syndrome[4, 5]. Furthermore, new research recently demonstrated an association between metabolic syndrome and psoriasis[6].

Ghrelin is an adipose-derived peptide formed of twenty-eight amino acids and mostly secreted by the stomach mucosa[7, 8]. It controls the release of growth hormones, energy expenditure, glucose homeostasis, body weight, and inflammation[9]. Additionally, through its influence on T cells and monocytes, it demonstrates strong inhibitory effects on proinflammatory mediators[10]. In psoriasis patients, serum ghrelin levels may be linked to clinical and metabolic changes[11].

Strong heritability for PsA is demonstrated by epidemiological research. This suggests that there may be individual risk loci for this autoimmune disorder[11]. Finding these loci may result in the development of new therapeutic targets and enhance the outcome by enabling early detection of PsA, which may avert irreparable joint degeneration[12].

The ghrelin gene is identified on the chromosome 3p25–26. Additionally, the ghrelin receptor gene has been found on chromosome 3q26–27. There are five exons in the human ghrelin gene, and exons 1 and 2 encode the twenty-eight amino acids that constitute the active part of ghrelin[13]. This gene encodes for the ghrelin hormone which suppresses inflammation and initiates an anti-inflammatory profile through taking action on the innate and adaptive immune systems[14]. Ghrelin gene polymorphisms have been studied in several autoimmune disorders, including rheumatoid arthritis (RA), where the A-501C SNP in the ghrelin gene is linked to an early-onset RA[15]. A recent study on the Turkish population reported that the rs34911341 polymorphism of ghrelin may be related to early-onset psoriatic skin disease[16].

Single nucleotide polymorphisms (SNPs) in the human ghrelin gene can ultimately result in abnormalities in the anti-inflammatory ghrelin protein[10].

Therefore, the potential disruption of ghrelin regulation may significantly influence the pathophysiology of PsA. However, there is limited data in the research on the potential role of ghrelin gene polymorphisms in PsA. To the best of our knowledge, this is the first study on the Egyptian population to assess the relation between the gene polymorphism rs34911341 and the susceptibility of PsA.

The purpose of the current research was to assess the possible role of ghrelin and its gene polymorphism (rs34911341) among PsA patients.

METHODOLOGY

Study design and sample size:

This case-control study was conducted at the Outpatient Clinics and Inpatient Unit at the Rheumatology and Rehabilitation Department, Zagazig University Hospitals- Egypt. The study was performed from November 2023 to October 2024. In our research, 126 subjects were included and categorised into 63 patients having PsA and 63 age and sex-matched healthy controls. The study was approved by the local ethical committee. Inclusion criteria involved patients having PsA who met the CASPAR classification criteria for PsA[17], both sexes and healthy control who are age and sex-matched and are able to give consent. However, exclusion criteria were patients with other seronegative spondyloarthropathies, patients with other autoimmune diseases: as RA, systemic lupus erythematosus or patients with arthritis and skin conditions comparable to psoriatic skin lesions like discoid eczema, seborrheic eczema.

Clinical assessment:

Thorough general and locomotor system examinations were performed. The skin was assessed for skin rash and the nails were evaluated for examination: pitting, leukonychia, crumbling, onycholysis, hyperkeratosis as well as splinter haemorrhages[18]. Dactylitis grading was according to Helliwell et al.[19]. Examination for enthesitis at sites of enthesis and tenderness at each site was graded according to Healy & Helliwell[20]. Patients were assessed for PsA activity by Disease activity index for psoriatic arthritis (DAPSA), Leeds enthesitis index (LEI) for enthesitis, and Leeds Dactylitis index (LDI). DAPSA consists of a number of tender and swollen joints, C reactive protein (CRP) level, and patient's assessment of disease activity and pain by 0-10 visual analogue scale[21]. The cut points for the disease activity are: (0-4) remission, (5-14) low disease activity, (15-28) moderate disease activity, (>29) high disease activity[22]. All patients were subjected to plain X-rays for both sacroiliac joints. Sacroiliitis grading was done according to Geijer et al[23] as the following: Grade 0: No change, Grade 1: Suspicious change, some joint margins blurring, Grade 2: Small localized areas with sclerosis or erosion or sclerosis without joint width change, Grade 3: Moderate or advanced sacroiliitis with erosions, sclerosis, narrowing, widening, or partial ankylosis, Grade 4: Severe abnormality with total ankylosis.

Laboratory investigations:

Routine Laboratory investigations:

We performed Complete blood count (CBC) on Sysmex xs 500i (Japan,sysmex), liver and kidney functions on Cobas 8000 autoanalyzer (Roche Diagnostics, Germany), Rheumatoid factor (RF) and CRP on Cobas 6000 auto analyser (Germany, Roche Diagnostics), ESR on vision ESR Analyzer (YHLO, China) and Measurement of Fasting Ghrelin serum level by ELISA kit (Kits were provided from Wuhan Fine Biotech Company (China) with Catalogue No. EH0355 named Human GHRL(Ghrelin)) as directed by the manufacturer's instruction.

DNA extraction:

By using the QIAamp DNA kit, we extracted DNA from EDTA blood following the manufacturer's protocol (QiagenHilden, Germany), By using primers for GHRL rs34911341 (346G/A) F: GCTGGGCTCCTACCTGAGC and R: GGACCCTGTTCACTGCCA, Amplification was performed in a twenty-five (25 ul) final volume containing 2 µl of genomic DNA, 1µl of each reverse and forward primers, 12.5 µl of the ready master mix and 8.5 µl nuclease-free water with cycling condition of initial denaturation step at 95˚C for 1 min then 35 cycles of denaturation at 95˚C for 30 sec, Annealing at 60˚C for 1 min, Extension at 72˚C for 1 min and last extension at 72˚C for 10 min using Gene Amp, thermal cycler, PCR system 2400 (AB applied biosystem, Perkin Elmer, USA) yielding 618 bp amplicon that was primary purified utilizing QIA quick (QIAGEN) PCR Purification Kit then, measurement of DNA concentrations by Qubit 3.0 (Fluorometer, life technology, Invitrogen, Malaysia). Cycle sequencing (secondary PCR) was performed on the primary purified product by utilising Big dye terminator ready reaction cycle sequencing kit V3.1 (Applied Biosystem, USA), in which amplification was performed in a 10 µl reaction mixture, containing 2 µl of Big dye terminator , 1ul of 5X sequencing buffer, 20 ng of PCR product, 1 µl of 3.2 Pmol of forward primer then deionized water was added to complete the reaction mixture to 20 µl using Gene Amp, thermal cycler, PCR system 2400 (AB applied biosystem, Perkin Elmer, USA) through cycling condition of denaturation at 96˚C for 1 min, then 25 cycles of amplification (96˚C for 10 sec, 60˚C for 5 sec and 60˚C for 4 min), then rapid thermal temperature was decreased to 4 °C and held until ready to secondary purification using Big dye X terminator purification kit, then, the secondary purified product was ready for DNA sequencing using 3500 Genetic Analyzer (Applied Biosystem, USA), eventually, the

sequencing results were interpreted by using Basic Local Alignment Search Tool (BLAST) website to find areas of local resemblance among sequences.

Statistical analysis:

Statistical analysis was accomplished utilizing the software SPSS (Statistical Package for the Social Sciences) version28. Categorical data was represented as frequency and percent then being compared using the chi-square test. Normality of data distribution was tested by Kolmogorov–Smirnov test. Then data was represented either as Mean±SD or median(interquartile-range) then independent sample t-test and Mann-Whitney test were used accordingly. For quantitative data between more than two groups, Kruskal-Wallis test and one-way ANOVA test were used. As the difference is significant, pairwise comparison and Bonferroni were accustomed to distinguish the difference individual groups. Pearson correlation was served to measure direction and strength of correlation. We utilized the ROC curve to define the best cut-off of certain quantitative measure in the diagnosis of specific medical conditions. The level of statistical significance was set at P<0.05. A highly significant difference was present if p≤0.001.

RESULTS

The study was conducted on 63 patients with PsA and 63 healthy controls. The baseline data of both groups illustrated no significant difference between the studied groups regarding age, gender, body mass index, and the ghrelin Gene SNP rs34911341 ($P > 0.05$). However, there was a significant difference between both groups regarding serum ghrelin (P<0.001) with significantly higher levels among the case group (Table 1).

Table 1: Baseline data of the studied groups:

	Case group N=63 (%)	**Control group N=63 (%)**	**χ^2**	**p**
Gender Male Female	 35 (55.6%) 28 (44.4%)	 29 (46%) 34 (54%)	1.143	0.285
	Mean ± SD	**Mean ± SD**	**t**	**p**
Age (year)	46.44 ± 11.77	43.49 ± 12.41	1.37	0.173
BMI (kg/m2)	27.51 ± 5.47	25.86 ± 4.47	1.856	0.066
Serum ghrelin levels	29.11 ± 7.6	17.72 ± 3.46	10.832	<0.001**
Gene SNP rs34911341 CC CT TT	 28 (44.4%) 19 (30.2%) 16 (25.4%)	 31 (49.2%) 16 (25.4%) 16 (25.4%)	χ^2 0105	 0.746

χ^2Chi square test t independent sample t test **p≤0.001 is statistically highly significant

The clinical types of PsA in our patients showed 57.1% polyarticular, 55.6% axial type, 17.5% oligoarticular, and 12.7% predominant DIP involvement. Additionally, 54% of the patients had eye affection and 71.4% had nail changes. The median disease durations of skin and joint affection in our patients were 10 and 4 years respectively. Patients were assessed for disease activity by DAPSA, Leeds Enthesitis index, Leeds Dactylitis index, and laboratory tests as shown in (Table 2).

Table 2: Clinico-laboratory parameters of the patient group:

	Median (IQR)	**Range**
Duration of skin affection	10 (8 – 16)	3 – 26
Duration of joint affection	4 (3 – 6)	1 – 13
Leeds Enthesitis Index (LEI).	0 (0-2)	0-4
Leeds Dactylitis index	0 (0 – 10.2)	0 – 13.4
DAPSA Low activity Moderate activity High activity	16.2(11.4 – 21.4) 29 30 4	5.3 – 37.1 46% 47.6% 6.3%
ESR (mm/hr)	33(21 – 45)	5 – 88
CRP	4 (3 – 8)	1 – 18
	Mean ± SD	
Uric acid (mg/dl)	6.46 ± 2.5	1.64 – 12.4
Fasting blood glucose (mg/dl)	82.63 ± 9.58	66 – 109
Triglycerides (mg/dl)	113.7 ± 46.05	55.5 – 233
Total cholesterol (mg/dl)	155.44 ± 34.28	89.8 – 204
HDL (mg/dl)	49.73 ± 10.42	27 – 65.6
LDL (mg/dl)	94.17 ± 34.02	41 – 190

About 48% of patients had moderate activity and 46% had low disease activity. Correlations between serum ghrelin and the studied parameters among the case group were represented in (Table 3).

Table 3: Correlation between serum ghrelin and the studied parameters among psoriasis patients

	r	p
Age (year)	0.027	0.833
BMI	-0.731	<0.001**
Duration of skin affection	-0.191	0.133
Duration of joint affection	0.156	0.221
Leeds Dactylitis index	-0.037	0.772
DAPSA	-0.697	<0.001**
ESR (mm/hr)	-0.455	<0.001**
CRP (mg/L)	-0.379	0.002*
Serum uric acid (mg/dl)	0.49	<0.001**
Fasting blood sugar (mg/dl)	-0.313	0.013*
Triglycerides (mg/dl)	-0.269	0.033*
Total cholesterol (mg/dl)	-0.579	<0.001**
HDL cholesterol (mg/dl)	0.332	0.008*
LDL cholesterol (mg/dl)	-0.667	<0.001**
	Median (IQR)	**Test**
Activity		
Low	32 (24.8 – 41.2)[2,3]	KW=31.333
Moderate	24.55(23.3 – 31)	P=<0.001**
High	21.3(19.05 – 29.33)	

r Pearson correlation coefficient *p<0.05 is statistically significant **p≤0.001 is statistically highly significant KW Kruskal Wallis test

A statistically significant negative correlation was found between serum ghrelin and all of the body mass index (BMI), CRP, ESR, DAPSA score, triglycerides (TG), fasting blood sugar (FBG), total cholesterol, and low-density lipoproteins (LDL). However, there were significant positive correlations with high-density lipoproteins (HDL) and serum uric acid. Serum ghrelin showed a significant negative correlation with PSA disease activity parameters and on doing a pairwise comparison among the disease activity grades, the difference was significant between patients with low activity and each other group. Accordingly, the ROC curve was done to assess the performance of serum ghrelin in detection of low disease activity (Figure 1).

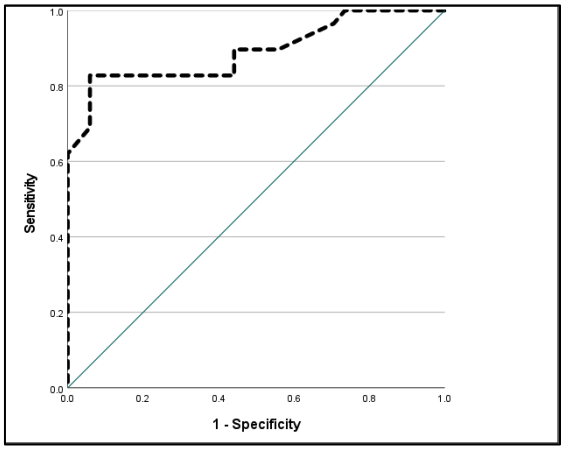

Figure (1) ROC curve showing the **performance of serum ghrelin in detection of low PsA disease activity.**

As shown in (Table 4), the best cut-off value of serum ghrelin in the diagnosis of low disease activity was ≥30.4, with the area under curve 0.891, sensitivity 82.8%, specificity 94.1%, and accuracy 88.9% (p<0.001).

Table (4) Performance of serum ghrelin in prediction of low disease activity:

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	p
≥30.4	0.891	82.8%	94.1%	92.3%	86.5%	88.9%	<0.001**

AUC area under curve PPV positive predictive value NPV negative predictive value **p≤0.001 is statistically highly significant

In studying the relation between gene SNP rs34911341 and the studied parameters among psoriasis patients (Table 5), there was a statistically significant relation between the gene SNP rs34911341 and BMI (P=0.028). A post hoc analysis reveals a significant difference between CC and CT. Additionally, there was a statistically significant relation between gene SNP rs34911341 and triglycerides levels (P= 0.005) and the difference was significant between CC and each other group. Furthermore, there was no significant relation between the gene and parameters of PSA disease activity.

Table (5): Relation between Gene SNP rs34911341 and the studied parameters among psoriasis patients

	CC (n=28)	CT (n=19)	TT (n=16)	F	p
	Mean ± SD	Mean ± SD	Mean ± SD		
Age (year)	49.43 ± 14.01	46.32 ± 6.53	41.38 ± 11.14	2.5	0.091
BMI	28.75 ± 5.08	24.89 ± 3.77	26.25 ± 5.53	**3.799**	**0.028***
Bonferroni	P_1 0.029*	P_2 >0.999	P_3 0.316		
	27.81 ± 8.73	28.71 ± 6.02	31.86 ± 6.82	1.511	0.229
Serum uric acid (mg/dl)	6.07 ± 2.64	6.27 ± 2.23	7.39 ± 2.47	1.521	0.227
Fasting blood sugar (mg/dl)	81.71 ± 10.12	83.26 ± 10.66	83.63 ± 7.45	0.249	0.78
Total cholesterol (mg/dl)	153.62 ± 40.59	154.26 ± 44.86	134.25 ± 37.15	1.362	0.264
HDL cholesterol (mg/dl)	45.24 ± 10.28	46.1 ± 8.19	42.46 ± 12.68	0.578	0.564
	Median (IQR)	Median (IQR)	Median (IQR)	KW	p
LDL cholesterol (mg/dl)	116(82.5 – 121)	99(70.7 – 107)	83.5(61 – 124.25)	4.553	0.103
Triglycerides (mg/dl)	80(76.5 – 117.3)	106(102.8 – 177)	114.5(107.8-176.8)	10.523	0.005*
Pairwise	P_1 0.007*	P_2 0.896	P_3 0.007*		
ESR (mm/hr)	36(27 – 46)	30(11 – 40)	32.5(16.3 – 45.3)	3.294	0.193
CRP (mg/L)	6.5(5 – 9)	4(3 – 6)	3(2.3 – 3.8)	16.354	<0.001**
Pairwise	P_1 0.033*	P_2 0.069	P_3 <0.001**		
Duration of skin affection	10(7.5 – 21.5)	11(9 – 13)	9(6.3 – 12.8)	1.924	0.382
Duration of joint affection	3(2 – 5)	5(4 – 6)	3(2.3 – 7.5)	2.237	0.327
Leeds Dactylitis index	0(0 – 10.2)	0(0 – 10)	0(0 – 8.03)	0.212	0.9
DAPSA	18.3(10.1 – 22.8)	15.6(11.9 – 18.3)	15.1(13.3 – 18.9)	0.939	0.625
Activity					
Low	13 (46.4%)	8 (42.1%)	8 (50%)	2.263	0.687
Moderate	12 (42.9%)	10 (52.6%)	8 (50%)		
High	3 (10.7%)	1 (5.3%)	0 (0%)		

F one way ANOVA test KW Kruskal Wallis test p1 difference between CC and CT p2 difference between CT and TT p3 difference between CC and TT *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

DISCUSSION

Ghrelin is a novel peptide hormone that has anti-inflammatory activity and plays a crucial role in many physiological and pathological conditions[24]. Serum ghrelin and its gene polymorphisms have been studied recently in many diseases and inflammatory conditions such as metabolic syndrome[1], hypertension[25], rheumatoid arthritis[15], and skin psoriasis[8]. In the present study, we evaluated the potential role of serum ghrelin and its gene SNP rs34911341 in PSA. A significantly higher level of serum ghrelin was detected in PSA patients in comparison with healthy controls. These results come in concordance with Farag et al[8] who proved significantly higher levels of serum ghrelin in non-obese psoriasis vulgaris patients. Similar results were also reported by[1, 25, 26]. Serum ghrelin levels showed significant negative correlations with the disease activity parameters like DAPSA, ESR, and CRP with significantly higher levels with lower activity grades. Similarly, Ucak et al.[1] and Farag et al[8] illustrated that serum ghrelin levels are significantly higher in milder forms of skin psoriasis. These results can be explained by the anti-inflammatory role of the serum ghrelin and suppression of the proinflammatory cytokines through downregulation of the TNF-α/NF-κB signaling[24, 26]. Additionally, Xia et al. [28] stated that ghrelin suppresses the proliferation of anti-CD3-activated murine T cells along with suppression of Th1 cytokines such as IL-1 and INF-γ.

Accordingly, we evaluated the performance of serum ghrelin in the prediction of low disease activity and found that at a cut-off value of ≥30.4 serum ghrelin was 82.8% sensitivities and 94.1% specific for detection of low PSA activity. Hence, we suggest that serum ghrelin could be a biological biomarker for predicting low disease activity in PsA patients. Interestingly, Qu et al[24] suggested that ghrelin peptide is a protective factor against psoriasis and could be a potential therapeutic target for better disease control.

Regarding the metabolic changes in the patient group, we found a significant negative correlation between serum ghrelin and the lipid profile encompassing triglycerides, total cholesterol, and LDL. However, there was a significant positive correlation between HDL and serum uric acid. Although FBG was normal in our patients, it also showed a negative correlation with the level of serum ghrelin. Similar results were found by Kelishadi et al[27] who studied the relationship between the ghrelin hormone and metabolic changes in obese children. He reported that as ghrelin levels increased, the odds of central obesity, high TG, and low HDL-C decreased. Additionally, Ucak et al reported a high percentage of metabolic syndrome in psoriasis patients which was correlated to the serum ghrelin levels[1].

The human ghrelin gene has been recently investigated for its variations and possible disease associations. Loft et al[12] studied the genetic variations in psoriasis and PSA and found that SNPs in the IL12B and TNF genes were related to the susceptibility of psoriasis. In the current study, we evaluated one of the ghrelin gene polymorphisms, SNP rs34911341, and found no association between the gene and the susceptibility of PsA. However, a significant relationship was reported between the BMI and gene polymorphism, especially CC and CT alleles. Furthermore, the CC allele showed a significant relation with the TG level. Likewise, Hinney and his colleagues identified four ghrelin gene sequence variants in the coding region that are related to the weight extremes[29]. These results support the role of ghrelin and its genes in obesity and metabolic syndrome which is a significant comorbidity in PSA patients.

In the study of the hand, we emphasized the essential role of ghrelin hormone in PSA and the associated metabolic syndrome. However, this study was performed in one centre and involved the same ethnic group. Wide genomic studies in different populations are strongly recommended to evaluate the different ghrelin gene susceptibilities for PSA.

CONCLUSIONS

Ghrelin hormone has a fundamental role in PSA and it could be a biological biomarker for prediction of low disease activity in PSA. Ghrelin gene polymorphism, SNP rs34911341, has no association with PSA; however, it could be associated with obesity and metabolic changes in psoriatic patients.

Abbreviations

BLAST: Basic Local Alignment Search Tool
BMI: Body mass index
CASPAR: Classification criteria for psoriatic arthritis
CBC: Complete blood count
CRP: C-reactive protein
DAPSA: Disease activity index for psoriatic arthritis.
DIP: Distal interphalangeal joint
DM: Diabetes mellitus
ESR: Erythrocyte sedimentation rate
FBS: Fasting blood sugar.
GHRL: Ghrelin
HDL: High density lipoproteins
IL-1: Interleukin 1
INF-γ: Interferon γ.
LDL: Low-density lipoproteins
LEI: Leeds enthesitis index
NCBI: National Centre for Biotechnology Information
NF-κB: Nuclear factor κB
PCR: Polymerase chain reaction
PsA: Psoriatic arthritis
RA: Rheumatoid arthritis.
SNPs: Single nucleotide polymorphism
SPSS: Statistical Package for the Social Sciences
TG: Triglycerides
TNF-α: Tumor necrosis factor-alpha

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Statements and Declarations

Conflict of interest: No conflict of interest.

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Consent to participate: A written informed consent was obtained from all participants.

Consent for publication: The authors provided consent for publication.

Data and materials availability: The data analyzed during the present research are not available in public owing to the General Data Protection Regulation (GDPR). However, on reasonable request, a small data set supporting the primary analyses is made available.

Ethics approval:

The study was approved by the Institutional Review Board No (IRB#: 11113-10-10-2023) at the Faculty of Medicine, Zagazig University Hospitals. This study was performed complying with the Code of Ethics of the World Medical Association (Declaration of Helsinki 1964) for studies on humans.

Authors' contributions

Authors' contributions R. A., R. H., M. S., D. K.: designed the study and participated in drafting the

article, A. S., D. K.: collection of data, R. A., A. S., D. K.: analysed and interpreted the data and shared the article revision, R. A., A. S., R. H., M. S.: shared in editing the manuscript and revising it. All authors have read and accepted the final version of the article.

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