Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2023.230698.2854 Volume 30, Issue 1.3, April 2024, Supplement Issue
Manuscript ID ZUMJ-2308-2854 (R1)
DOI 10.21608/ZUMJ.2023.230698.2854
ORIGINAL ARTICLE

Receptor of Advanced Glycated End Products Gene Polymorphism in Patients with Rheumatoid Arthritis

Lamiaa Abdel Wahaab Mohammad[1], Ghada S. Nageeb[2], Manar Abdullah Soliman Nassar[1*], Safaa M. Elalawi[1]
[1] Clinical Pathology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt
[2] Rheumatology and rehabilitation Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

[*]Corresponding author:
Manar Abdullah Soliman Nassar,

Email:
dr.manarabdullah.1988@gmail.com

Submit Date 21-08-2023
Revise Date 02-09-2023
Accept Date 2023-09-05

ABSTRACT

Background: Through its capacity to intensify inflammatory pathways, Rheumatoid arthritis (RA) has been connected to the receptor for advanced glycation end products (RAGE). So, in those with rheumatoid arthritis, the RAGE gene polymorphism may be a significant indicator of disease activity. Our aim is illustration of the role of RAGE gene polymorphism (G82S) in susceptibility of rheumatoid arthritis.**Methods:** Thirty individuals were used in this case control study, which was conducted at the Zagazig University hospitals' Clinical Pathology, Rheumatology, and Rehabilitation departments after obtaining their written agreement for ethical reasons. The participants were split up into two groups: fifteen RA cases and fifteen healthy volunteers who acted as the control group. A molecular investigation of the RAGE gene's glycine-to-serine (G82S) polymorphism was done for genotyping.
Results: Rheumatoid arthritis patients have allele G levels that are 7 times greater than those in the control group, with a 95% CI of 1.38 to 35.5. Significant difference: p=0.009.**Conclusions:** The RAGE gene polymorphism (G82S) with allele G was higher in rheumatoid arthritis patients than the control group. Sadly, we were unable to discover a link between gene variation and disease activity.
Keywords: Rheumatoid arthritis; polymorphism; RAGE.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory condition causes the deterioration of bone and cartilage in addition to extra-articular consequences such atherosclerotic vascular disease and early mortality [1]. RA patients are at high risk of developing cardiovascular disease (CVD), as inflammation plays a pivotal role in the pathogenesis of CVD .Therefore, the patients with RA have approximately a double risk of atherosclerotic CVD, stroke, heart failure, and atrial fibrillation (AF) compared with the normal population [2].AGEs are a group of substances that are produced when proteins, lipids, or nuclear acids are non-enzymatically glycated, sometimes as a result of oxidative stress. Increased AGE accumulation has been observed in RA. By binding to the receptor for advanced glycation end products (RAGE), AGEs cause inflammation and help in the development of atherosclerosis [3, 4].

RA also results in an increase in other pro-inflammatory RAGE -ligands, such as high mobility group box 1 (HMGB-1) and Sl00 calgranulins [5].Soluble RAGE (sRAGE) can prevent the binding of RAGE-ligands. It has been proposed that this RAGE isoform, which is generated by alternative splicing or shedding, serves as a bogus receptor. Recombinant sRAGE treatment prevented development of atherosclerosis in a mouse model of accelerated atherosclerosis and stabilized already present atherosclerosis [9].

RAGE is a member of immunoglobulin superfamily which is encoded in class III region of major histocompatibility complex. One V type domain, two C type domains, a transmembrane domain, and a cytoplasmic tail make up this multiligand receptor. The majority of extracellular ligand binding is accomplished by the V domain, which has two N-glycosylation sites. It is believed

that the cytoplasmic tails are crucial for intracellular signaling [7-9].

Previous studies revealed that RAGE was also a receptor for signal transduction pro-inflammatory S100/calgranulins, amphoterin [or high mobility group box 1 (HMGB1)], amyloid peptide, and sheet fibrils, in addition to being initially described as a receptor for AGEs [10, 11].

RAGE functions as a master switch that activates Nuclear factor-kappaB (NF-KB), inhibits a variety of endogenous auto regulatory functions, and converts protracted pro-inflammatory signals into chronic cellular malfunction and disease. Its activation is accompanied by a large number of faulty proteins in biological tissues and fluids and is directly linked to a number of ailments, including allergies, Alzheimer's, rheumatoid arthritis, and urogenital problems [12].

It has previously been shown that a polymorphism of the gene encoding RAGE located within the V-type immunoglobulin domain of RAGE, which results in a glycine to serine substitution at amino acid position 82, is in linkage disequilibrium with HLA-DR4. It was therefore not surprising that the Ser82 allele was increased in RA subjects [10]. The aim of this study was to evaluate the ser 82 polymorphism in RA patients and to access the relationship between ser 82 allele and disease activity in RA patients.

Methods

Thirty individuals were included in this case control study, which was conducted at the Zagazig University hospitals' Clinical Pathology, Rheumatology, and Rehabilitation departments after obtaining their written agreement for ethical reasons.

The study's protocol was approved by both the regional ethics committee and the Institutional Review Board [IRB], Faculty of medicine, Zagazig University (n: 5127-15-1-2019). The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

The cases were 15 patients with rheumatoid arthritis who were identified using the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA [13]. Patients from other regions who had autoimmune disorders or cancer were excluded.Our study included 15 RA patients, their mean age was 41.93±11.5 ranged from 27 to 60 years with 80% of patients female. The control group were 15 healthy subjects, their mean age was 41.47±11.18, ranged from 28 to 59 years with 73.3% of patients female.All groups were subjected to: history taking, general and local examination, laboratory investigations: RF, CRP by immunoturbidimetric assay on Cobas 6000, c501 module and Liver and kidney function tests was done by Cobas 6000, c501 module, Roche Diagnostic, Mannheim, Germany. The main steps of the sequencing process were extraction, amplification, first purification, cycle sequencing, second purification, and then injection.

Molecular investigation:

By using direct sequencing and HITACHI 3500 Genetic Analyzer, a molecular analysis of the glycine 82 serine (G82S) polymorphism of the RAGE gene was performed for genotyping.

The QIAamp DNA Blood Mini Kit (QIAGEN) was used to extract DNA, and the G82S specific primers (Forward 5'-AGCTGGCCCTGGCACTGACTGCTCT-3' and Reverse 5'-ATGGAAACACCTTGCTTCTTCTTCTCTCTC TC-3') were used to amplify up the extracted DNA. PCR amplification was performed in a reaction mixture, containing 6 ul of genomic DNA, 12 ul nuclease free water, 1 ul of 10 pmol of both forward and reverse primers, 12.5ul of the ready master mix (Top Taq Master Mix Kit QIAGEN). Then, the cycle sequencing product underwent secondary purification using a large dye x terminator purification kit after being first purified using QIAquick PCR Purification (QIAGEN). PCR was performed using thermal cycler (Biometra T. professional) with cycling condition of initial denaturation at 95˚C for 1min, 35 cycles of denaturation at 95 ˚C for 1min, annealing at 61˚C for 40 seconds, extension at 72˚C for 10sec., followed by a final extension at 72˚C for 7 min. The analysis of the sequencing data follows the injection of pure amplified G82S into the Genetic Analyzer 3500 (Applied Biosystem, USA).

Statistical Analysis

Using SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA 2011, all data were gathered, tabulated, and statistically evaluated). unbiased samples It was done using the Chi-square test, Fisher Exact test, Student's t test, and Mann Whitney U test.

RESULTS

In the current study, there was statistically insignificant difference of rheumatoid arthritis patients &controls regarding age and sex p>0.05 **(Table 1)**. The main complaint was pain in both hands 20% among the studied patients **(Table 2)**. The median disease duration in RA patients was 6 years with range from three months to 16 years. Morning stiffness range from none to > 1 hour. The most frequent manifestation was eye affection (46.7%), followed by osteophyte,

deformity, skin affection (20.0% for each complaint), then erosion and synovitis (6.7% for each complain) **(Table 3)**. Most of patients treated with Methotrexate alone 60.0% or with Hydroxychloroquine33.3% only one patients (6.7%) treated by Sulphasalazine **(Table 4)**. There was statistically insignificant difference between rheumatoid arthritis patients &controls regard their genotyping. Allele G are 7 times higher among the rheumatoid arthritis patients compared to control group with 95% CI=Confidence interval 1.38 to 35.5, the difference significant was p=0.009 **(Table 5)**. Hb (g/dl) was greater in the control group compared to the rheumatoid arthritis patients with a statistically significant difference of p=0.0001, while activity indicators and serology tests were higher in the case group compared to control group **(Table 6)**. Rheumatoid arthritis patients' genotyping, sex distribution, clinical symptoms, and lab results did not differ in a statistically significant way **(Table 7)**.

Table (1): Demographic data, of rheumatoid arthritis patients &control groups

Variables	Studied groups		Test of sig	p-value
	rheumatoid arthritis n=15	Control n=15		
Age per years Mean ±SD Median (range)	41.93±11.5 40(27-60)	41.47±11.18 39(28-59)	t=0.11	0.91
Sex n(%)				
Females	12(80)	11(73.3)	χ^2=0.18	0.66
Males	3(20)	4(26.7)		

χ2=Chisquare test, t Student t test, p>0.05 non significant.

Table (2): Frequency distribution of complaint among studied rheumatoid arthritis patients:

Complaint	Number of patients	%
Back pain	1	6.7
Both shoulders pain	1	6.7
lower back pain	1	6.7
Pain at most of joint	1	6.7
Pain in both hands	3	20.0
Pain in both knee	1	6.7
pain in elbow& wrist	1	6.7
Pain in hip joint	1	6.7
Pain in most joints	1	6.7
Pain in PIPS,HCPS	1	6.7
Pain in Rt elbow	1	6.7
Pain in Rt. wrist	1	6.7
Pain in wrist and ankle	1	6.7
Total	15	100.0

Table (3): Frequency of clinical manifestations among studied rheumatoid arthritis patients

Variables	
Duration of disease per years Median (range)	6 years (3 months-16 years)
Morning stiffness/minute Median (range)	15(0-70)
Number of tender joints Median (range)	12(0.00-28)
Number of swollen joints Median (range)	1(0.00-8)

DAS Median (range)	5.2(2.2-6.1)			
	Yes		**No**	
	n.	**%**	**n.**	**%**
Erosion	1	6.7	14	93.3
Synovitis	1	6.7	14	93.3
Eye affection	7	46.7	8	53.3
Skin affection	3	20.0	12	80.0
Osteophyte	3	20.0	12	80.0
Deformity	3	20.0	12	80.0

Table (4): Frequency distribution of Treatment of studied rheumatoid arthritis patients:

Treatment	**n.**	**%**
Methotrexate	9	60.0
"Hydroxychloroquine combined Methotrexate	5	33.3
Sulphasalazine	1	6.7
Total	15	100.0

Table (5): Receptor of Advanced Glycated End Products Gene Polymorphism and allele in Patients with Rheumatoid Arthritis &control group

Variable	**Studied groups**		**F**	**Odds(CI)**
	Rheumatoid Arthritis group n=15	**Control group n=15**		
Genotyping n(%)	5(33.3)	1 (6.7)	p= 0.17	7(0.71-69.4)
Genotype G_G				
Genotype C_C	10(66.7)	14(93.3)		
ALLE n(%)				
ALLE G	10(33.3)	2 (6.7)	6.67	7(1.38-35.5)
ALLE C	20(66.7)	28(93.3)	P=0.009	

F=Fisher exact test, χ2=Chisquare test, odd ratio (95% CI=Confidence interval).

Table (6): Laboratory features rheumatoid arthritis patients versus control

Variables	**Studied groups**		**U test**	**p**
	Cases	**Control**		
Disease activity				
ESR (1st H) Median (Range)	36(5-101)	4(3-7)	4.51	0.0001
CRP(mg/L Median (Range)	13(4-70)	2(0.4-3.4)	4.67	0.0001
CBC				
WBCs×1000 Median (Range)	7.2(4.3-15.3)	7(5.1-10.5)	0.104	0.917
RBCs Mean ±SD	4.37±0.49	4.26±0.65	t=0.504	0.62
Hb(g/dl) Mean ±SD	10.4±1.09	12.37±0.69	t=5.9	0.0001
PLT Median (Range)	231(133-446)	210(155-390)	0.33	0.740
Serology test				

RF(u/ml) Median (Range)	65(4.9-1383)	5.4(3.8-9.5)	4.19	0.0001
anti CCP Median (Range)	189(6-337)	6.2(3.3-9.5)	4	0.0001
Renal function				
Urea Median (Range)	26(15-53)	28(17-40)	0.416	0.678
Creatinine Mean ±SD	0.83±0.25	.79±0.13	t=0.46	0.65
Liver function				
Albumin Mean ±SD	3.97±0.51	4.04±0.42	t=0.39	0.69
ALT Median (Range)	20(9-53)	20(11-41)	0.166	0.868
AST Median (Range)	22(9-48)	22(10-31)	0.062	0.950

p<0.05 significant t= student t test U Mann-Whitney U test of sig

Table (7): Relation between genotyping and severity parameters of studied rheumatoid arthritis patients.

	Genotyping				**χ^2**	**p-value**
	C_C genotyping n.10		**G_G genotyping n.5**			
	No.	**%**	**No.**	**%**		
Erosion						
No	9	90.0	5	100.0	f	0.99
Yes	1	10.0	0	0.0		
DAS28 level						
Remission	2	20.0	0	0.0		
low disease activity	2	20.0	0	0.0	χ^2=3.56	0.31
Moderate disease activity	1	10.0	2	40.0		
Severe disease activity	5	50.0	3	60.0		
Anticcp level						
Abnormal	6	60.0	4	80.0	f	0.6
Normal	4	40.0	1	20.0		

χ 2=Chisquare test, f= fisher Exact test, p>0.05 non significant

DISCUSSION

RAGE has been discovered as a potential candidate molecule affecting the body's reaction to chronic inflammation and autoimmune. In addition to RA inflammation and the formation of autoantibodies, soluble RAGE has been linked to traditional vascular risk factors for end organ damage. According to these results and its role as a RAGE decoy molecule, RAGE activity promotes the co-development of joint and vascular disease in rheumatoid arthritis patients [5].In 2022 Holms [13] found that RAGE and advanced glycation end products frequently accumulate in the joints of RA patients, which increases the immune/inflammatory response. Human synovial fibroblasts reportedly express RAGE, primarily in the intima of the synovium. Inflammatory foci may develop AGEs as a result of oxidation or active myeloperoxidase pathways, according to recent investigations. AGEs, through RAGE, may stimulate pro-inflammatory mechanisms, therefore increasing inflammatory effects in chronic inflammatory disorders [14].In the study performed by Rashed et al. [16] who investigated that the RAGE gene has four polymorphisms, the functional dimorphism Gly82-Ser is the most prevalent. Through nuclear factor of kappa B (NF-KB) and mitogen-activated protein (MAP) kinases, Ser82 improves receptor signaling. Ser82's higher occurrence in RA may be explained by linkage disequilibrium with the HLA-DRB1*0401 allele, which is linked to the disease.

Rashed et al. [16] investigated the G82S polymorphism in RA patients and healthy people. It was discovered that RA patients had much greater frequencies of the gene (G82S) polymorphism than controls: 22 out of 33 RA patients, 5 of whom were homozygous for the RAGE serine82 variant, and 5 out of 16 controls, only one of whom was homozygous for the RAGE G82S allele. A variation in the RAGE gene's V type immunoglobulin domain, which changes amino acid position 82 from glycine to serine, has been demonstrated to be in linkage disequilibrium with the HLA-DR4 gene (17). So, it was not surprising that RA sufferers had a higher Ser82 allele (15).

It is possible that this variation in the RAGE gene, along with others associated to it, affects the splicing of the receptor's endogenously secreted C-truncated form or one's susceptibility to matrix metalloproteinase's cleavage of RAGE on cell surfaces, which may change the ratio of soluble to membrane RAGE [5]. In the study of Carroll et al. [18] The RAGE Ser82 allele, which is in linkage disequilibrium with the RA susceptibility allele HLA-DRB1*0401, was present in 20% of RA patients. They reported that RA patients are more likely than the general population to have a Gly82Ser polymorphism in the RAGE gene, which is linked to increase RAGE signaling. The receptor of Advanced Glycated End Products Gene Polymorphism in Patients with Rheumatoid Arthritis with g82s was explored in the current study. We discovered two genotypes: the first genotype, genotype G-G, was present in 33.3% of patients, and the second genotype, genotype C-C, was present in 66.7% of cases. In contrast, 6.7% of the controls in the control group had the genotype G-G, and 93.3% of controls had the genotype C-C. Regarding genotyping, there was no discernible difference between the two groups.

With a 95% CI=Confidence interval of 1.38 to 35.5, allele G are 7 times more prevalent in the current study's rheumatoid arthritis patients compared to the control group. The variation was substantial. In the current study, there was statistically insignificant difference between rheumatoid arthritis patients and controls regarding their genotyping.

Mokbel et al. [10] claimed that differences in the glycine82serine (G82S) allele that did not reach statistical significance between patients and controls were discovered using RAGE gene genotyping. Contrary to our findings, RA patients were more likely than healthy controls to have the RAGE gene Gly82Ser polymorphism (RAGE 82Ser) [15].

Regarding clinical symptoms and DAS, there was no discernible difference between patients with CC genotyping and those with GG genotyping in the current study. This came in agreement with Vytasek et al. [19] They failed to discover a link between the polymorphism and clinical presentation. While our finding in disagreement with Mokbel et al. [10] researchers discovered a link between gene variation and disease activity as shown by multiple sclerosis (MS) and CRP in RA patients. Our research showed that the clinical symptoms of rheumatoid arthritis patients varied according to genotype type, showing up as synovitis 10%, eye 50%, skin 20%, and osteophyte 20% in genotype C-C and no synovitis, eye 40%, skin 20%, and osteophyte 20% in genotype G-G.

Regarding laboratory indicators, there was no discernible difference between patients with genotypes G-G and C-C in the current investigation. This came in agreement with Vytasek et al. [19] who did not discover a link between the polymorphism and higher inflammatory levels (CRP and ESR). In disagreement with our study, Mokbel et al. [10] found that gene polymorphism is related to CRP. Also results of the Rashed et al. [16] revealed a correlation between gene polymorphism and the disease activity in RA patients as measured by CRP.

According to our findings, there was no discernible difference in terms of rheumatoid arthritis severity measures between patients with genotypes G-G and C-C. This came in agreement with Vytasek et al. [19] and Mokbel et al. [10] who failed to discover a link between the polymorphism and DAS.

Regarding age, there was no discernible difference between the two groups. Our findings indicated that women are four times more likely than men to develop rheumatoid arthritis. This result was in agreement with results of Areskoug-Josefsson et al. [20], they said that women have rheumatoid arthritis three times as often as men do in middle age.

In the current study, the most common complaint from patients was pain in both hands 20%, the morning stiffness ranged from none to >1 hour, and the most frequent manifestation was eye affection in the form of dryness (46.7%), followed by osteophyte, deformity, skin affection in the form of rheumatoid nodules (20.0% for each complaint), then erosion and synovitis (6.7% for each complain). These results agreed with results of Turesson [21] who reported that rheumatoid nodules are the most frequent skin manifestations (20%) in chronic RA which are frequently

associated with episcleritis, pleural and pericardial effusion while occular manifestations in the form of keratoconjunctivitis sicca is the most frequent occurred and usually affects at least 10% of patients. It is frequently observed together with xerostomia.

CONCLUSIONS

In conclusion, our research showed that rheumatoid arthritis patients have an allele G of RAGE gene polymorphism (G82S) 7 times higher than the control group. Sadly, we were unable to discover a link between gene variation and disease activity.

Conflicts of Interest: None.
Financial Disclosures: None.

REFERENCES

1. **Gazar YA, Gamal M, Ghait MM**. Relationship Between Serum Level of Homocysteine, Leptin and Neopterin and Disease Activity in Rheumatoid Arthritis patients with or without Extra-articular Manifestations. MJMR., 2020; 31(4), 342-9.
2. **Argnani L, Zanetti A, Carrara G, Silvagni E, Guerrini G et al.** Rheumatoid Arthritis and Cardiovascular Risk: Retrospective Matched-Cohort Analysis Based on the RECORD Study of the Italian Society for Rheumatology. Front. Med. 2021; 8, 745601.
3. **Chen JH, Lin X, Bu C, Zhang X.** Role of advanced glycation end products in mobility and considerations in possible dietary and nutritional intervention strategies. Nutr. Metab., 2018; 15(1), 72.
4. **Egaña-Gorroño L, López-Díez R, Yepuri G, Ramirez LS, Reverdatto S et al.** Receptor for advanced glycation end products (RAGE) and mechanisms and therapeutic opportunities in diabetes and cardiovascular disease: insights from human subjects and animal models. FRONT CARDIOVASC MED., 2020; 37.
5. **Chen YS, Yan W, Geczy CL, Brown M A, Thomas R.** Serum levels of soluble receptor for advanced glycation end products and of S100 proteins are associated with inflammatory, autoantibody, and classical risk markers of joint and vascular damage in rheumatoid arthritis. Arthritis Res Ther., 2009; 11, 1-11.
6. **Scavello F, Zeni F, Tedesco CC, Mensà E, Veglia F et al.** Modulation of soluble receptor for advanced glycation end-products (RAGE) isoforms and their ligands in healthy aging. Aging (Albany NY), 2019; 11(6), 1648.
7. **Hudson BI, Kalea AZ, del Mar Arriero M, Harja E, Boulanger E, et al.** Interaction of the RAGE cytoplasmic domain with diaphanous-1 is required for ligand-stimulated cellular migration through activation of Rac1 and Cdc42. JBC., 2008; 283(49), 34457-68.
8. **Riuzzi F, Sorci G, Sagheddu R, Chiappalupi S, Salvadori L, Donato R.** RAGE in the pathophysiology of skeletal muscle. J Cachexia Sarcopenia Muscle, 2018; 9(7), 1213-34.
9. **Prantner D, Nallar S, Vogel SN.** The role of RAGE in host pathology and crosstalk between RAGE and TLR4 in innate immune signal transduction pathways. FASEB journal, 2020;34(12), 15659.
10. **Mokbel A, Rashid L, Al-Harizy R.** Decreased level of soluble receptors of advanced glycated end products (sRAGE) and glycine82serine (G82S) polymorphism in Egyptian patients with RA. Egypt. Rheumatol., 2011; 33(1), 53-60.
11. **Chhipa AS, Borse SP, Baksi R, Lalotra S, Nivsarkar M.** Targeting receptors of advanced glycation end products (RAGE): Preventing diabetes induced cancer and diabetic complications. Pathology-Research and Practice, 2019;215(11), 152643.
12. **Bengmark S.** 22 Modified Amino Acid-Based Molecules: Accumulation and Health Implications. J. Health Pollut., 2011; 382.
13. **Holms RD.** Long COVID (PASC) Is Maintained by a Self-Sustaining Pro-Inflammatory TLR4/RAGE-Loop of S100A8/A9> TLR4/RAGE Signalling, Inducing Chronic Expression of IL-1b, IL-6 and TNFa: Anti-Inflammatory Ezrin Peptides as Potential Therapy. Immuno, 2022; 2(3), 512-33.
14. **Monu, Agnihotri P, Biswas S.** AGE/non-AGE glycation: An important event in rheumatoid arthritis pathophysiology. Inflamm., 2022; 45(2), 477-496.
15. **Hofmann MA, Drury S, Hudson BI, Gleason MR, Qu W, et al.** RAGE and arthritis: the G82S polymorphism amplifies the inflammatory response. Genes Immun., 2002;3(3), 123-135.
16. **Rashed L, Talaat R, Al-Harizy RM, Nabil A, Kamel A.** Correlation between Level of Soluble Receptors of Advanced Glycated End Products (sRAGE) and Gene Polymorphism of Glycine 82 Serine (G825) in Patients with Rheumatoid Arthritis. Egypt. J. Med. Microbiol., 2009; 18(4).
17. **Prevost G, Fajardy I, Fontaine P, Danze PM, Besmond C.** Human RAGE GLY82SER dimorphism and HLA class II DRB1-DQA1-DQB1 haplotypes in type 1 diabetes. Eur. J. Immunol., 1999; 26(5), 343-348.
18. **Carroll L, Frazer IH, Turner M, Marwick TH, Thomas R.** Receptor for advanced glycation end products Glycine 82 Serine polymorphism and risk of cardiovascular events in rheumatoid arthritis. Arthritis Res Ther, 2007; 9(2), 1-8.

19. **Vytášek R, Šedová L, Vilím V.** Increased concentration of two different advanced glycation end-products detected by enzyme immunoassays with new monoclonal antibodies in sera of patients with rheumatoid arthritis. BMC Musculoskelet. Disord., 2010; 11, 1-11.
20. **Areskoug-Josefsson K, Öberg UA.** literature review of the sexual health of women with rheumatoid arthritis. Musculoskelet. Care., 2009; 7(4), 219-226.
21. **Turesson C.** Extra-articular rheumatoid arthritis. Current opinion in rheumatology, 2013; 25(3), 360-366.

To Cite:

Mohammad, L., Nageeb, G., Soliman Nassar, M., Elalawi, S. Receptor of Advanced Glycated End Products Gene Polymorphism in Patients with Rheumatoid Arthritis. *Zagazig University Medical Journal*, 2024; (207-214): -. doi: 10.21608/zumj.2023.230698.2854