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Advanced glycation end products and their receptors level among type II diabetes mellitus in Iraq: A Case-Control Study

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Abstract.

Objective: To detect if there is any association between serum level of AGE and RAGEwith occurrence and severity of diabetic peripheral neuropathy. **Patients and method:** The study include 149 patients with type 2 diabetes, those patients recruited from diabetic center in Marjan medical city from Babylon governorateand diabetic center in Al-Sadr medical city from Alnajaf Alashrafgovernorate in the middle of Iraqduring the period from June 2019 to April 2020 .The patients is divided in to 2 group(group I with neuropathy and group II without neuropathy) according to the presence or absence of peripheral neuropathy depending on clinical assessment and results of neurophysiologic studies including conductive velocity, distal latency, amplitude for both sensory and motor nerves of upper and lower limbs. The results were analyzed in relation to AGE and RAGE blood level and compared with matched control group. Both patients and controls sent for biochemical assessment including random blood sugar, glycated hemoglobin. **Results:** The study found that the serum level of AGEwas significantly higher in patients with diabetic neuropathy than in patients without neuropathy (4146.86±2171.87 VS1299.78±1098.33pg/ml) **P <0.001**.The study also found that the level of RAGE was also significantly higher in patients with DPN than in patients without DPN (2945.12±1378.08 VS 1185.47±724.79 pg/ml**) P <0.001.**The serum level of AGE and RAGE constantly and significantly increased with the severity of diabetic peripheral neuropathy. **Conclusions:** There is significant association between AGE & RAGE serum level with occurrence and severity of diabetic peripheral neuropathy.

Keywords: Receptors, advanced glycation, end products, diabetic peripheral neuropathy

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Introduction

Diabetes mellitus is a clinical syndrome characterized by hyperglycemia caused by absolute or relative deficiency of insulin. Insulin deficiency affects the metabolism of carbohydrate, protein, fat and can cause significant disturbance of water and electrolyte

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homeostasis; death may result from acute metabolic decompensation (Davidson, 2018). Longstanding metabolic derangement is associated with functional and structural changes in many organs, particularly those of the vascular system, which lead to the clinical 'complications' of diabetes. These characteristically affect the eye, the kidney and the nervous system [1,2].

The molecular mechanisms involved in the development of Diabetic peripheral neuropathy is a complex process that includes activation of the polyol pathway, exaggerated oxidative stress, overactivity of protein kinase C and increased formation of advanced glycation end products in the presence of hyperglycemia. In addition, long-term hyperglycemia accelerates the formation and accumulation of advanced glycation end products and leads to the over-expression of their cellular receptors in diabetes [3].

The receptor for advanced glycation end products, a multi-ligand member of the immunoglobulin super family of transmembrane cell surface molecules, is the best characterized receptor for advanced glycation end products [4]. The activation of the receptor by advanced glycation end products plays a major role in the pathogenesis of diabetic vascular complications [5].

A number of receptor isoform have been found human. Among them, three major mRNA variants of receptor have been identified, encoding the full-length receptor which has full signaling and advanced glycation end products -binding potential, N-truncated receptor which is a membrane-bound isoform that contains no advanced glycation end products -binding domain and C-truncated sRAGE (soluble form of receptor) which has advanced glycation end products -binding properties in the absence of a signaling cascade [6].

The soluble forms of the receptor found in the circulation can act as a decoy for receptor ligands and blockage of receptor using C-truncated sRAGE ameliorates diabetic vascular complications in animal models.Hence modulating sRAGE is a novel means to protect tissues against the toxic effects of advanced glycation end products [7].

The cell types which express receptor for advanced glycation end products include endothelium, monocytes/macrophages, T lymphocytes, neuronal cells and glomerular epithelial cells [8].

This study conducted to evaluate the level of AGE and RAGE among type II DM Iraqi patients in relation to occurrence and severity of DNP.

Patients and method

The study include 149 patients with type 2 diabetes, those patients recruited from diabetic center in Marjan medical city from Babylon governorate and diabetic center in Al-Sadr medical city from Alnajaf Alashraf governorate in the middle of Iraqduring the period from June 2019 to April 2020 .The patients was divided in to 2 group according to the presence or absence of peripheral neuropathy depending on clinical assessment and results of neurophysiologic studies , those withperipheral neuropathy (group I) including 91 patients(61%) as patients group, and those without peripheral neuropathy (group II) ,58 patients (39 %) as control group. All participants (patients and control) underwent full

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assessment including detailed history and comprehensive physical examinations done by expert neurologist looking especially for signs of peripheral neuropathy.All participants underwent neurophysiological assessment by expert neurophysiologist (conductive velocity, distal latency, amplitude.) for both sensory and motor nerves of upper and lower limbs. Both patients and controls sent for biochemical assessment (random blood sugar, glycated hemoglobin, advanced glycation end products and receptors for advanced glycation end products). Group 2 patients (with DPN) classified in to mild, moderate and severe DPN depending on Toronto clinical neuropathy score (TCNS), the system was first adopted by a research group in Toronto for the screening of DPN. The TCSS (Table 1) composed of three mainparts: symptom scores, reflex scores and sensory test scores. The minimum score is 0 point while the maximum score is 19 points. The criteria of classification for DPN have also been proposed according to the TCSS score: 0-5 points, no DPN,6- 8 points, mild DPN; 9- 11 points, moderate DPN; and 12 - 19 points, severe DPN [9].

Table 1 Toronto clinical scoring system (TCSS)

TCSS items		Description
Symptoms score	Pain	0 = absent, 1 = present
	Numbness	0 = absent, 1 = present
	Tingling	0 = absent, 1 = present
	Ataxia	0 = absent, 1 = present
	Upper-limb symptoms	0 = absent, 1 = present
Reflex score	Knee reflexes	Score for each side: 0 = normal, 1 = reduced, 2 = absent
	Ankle reflexes	Score for each side: 0 = normal, 1 = reduced, 2 = absent
Sensory test score	Pinprick	0 = normal, 1 = abnormal
	Temperature	0 = normal, 1 = abnormal
	Light touch	0 = normal, 1 = abnormal
	Vibration sense	0 = normal, 1 = abnormal
	Position sense	0 = normal, 1 = abnormal

Measurement of Advanced glycation end products (AGE):

The preparation of the reagents included dilution of the wash buffer concentrate to 1X with de-ionized water and stirred to homogeneity. Immediately before use, the Anti-AGE antibody diluted 1:1000 and secondary antibody 1:1000 with assay diluent. The diluted solution is not stored.

The preparation of standard curve includes:

1- The reduced 10 µg/mL BSA and AGE-BSA Standards are freshly prepared by diluting the 1 mg/mL BSA standards in 1X PBS. Example: Add 20 µL to 1.980 mL of 1X PBS.

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2- A series of AGE-BSA standards is prepared.

The assay protocol included:

1- Unknown samples are prepared according to the preparation of samples section above. Each 10 µg/mL protein sample and BSA Standard should be assayed in duplicate or triplicate.
2- 100 µL of the 10 µg/mL protein samples or prepared BSA standards are added to the 96-well Protein Binding Plate, and then incubated at 37ºC for at least 2 hours or 4ºC overnight.
3- 200 µL of assay diluent are added per well and incubated for 1-2 hours at room temperature on an orbital shaker.
4- The wells are washed 3 times with 250 µL of 1X wash buffer with thorough aspiration between each wash. After the last wash, the wells are emptied and tapped micro well strips on absorbent pad or paper towel to remove excess 1X wash buffer.
5- 100 µL of the diluted Anti-AGE antibody are added to all wells and incubated for 1 hour at room temperature on an orbital shaker. The strip wells are washed 3 times according to step 4 above.
6- 100 µL of the diluted secondary antibody-HRP conjugate are added to all wells and incubated for 1 hour at room temperature on an orbital shaker. Wash the strip wells 5 times according to step 4 above.
7- 100 µL of substrate solution are added to each well, including the blank wells and Incubated at room temperature on an orbital shaker. Actual incubation time may vary from 2-30 minutes.
8- The enzyme reaction is stopped by adding 100 µL of Stop Solution to each well. Results should be read immediately (color will fade over time).
9- Absorbance is read for each well on a microplate reader using 450 nm as the primary wave length. Use the reduced BSA standard as absorbance blank.

Measurement Serum level of Receptor for advance Glycation end products:

Test principle

The ELISA kit uses the Sandwich-ELISA principle. The micro ELISA plate provided in this kit has been pre-coated with an antibody specific to Human AGER. Standards or samples are added to the micro ELISA plate wells and combined with the specific antibody. Then a biotinylated detection antibody specific for Human AGER and Avidin-Horseradish Peroxidase (HRP) conjugate are added successively to each micro plate well and incubated. Free components are washed away. The substrate solution is added to each well. Only those wells that contain Human AGER, biotinylated detection antibody and Avidin-HRP conjugate will appear blue in color. The enzyme-substrate reaction is terminated by the addition of stop solution and the color turns yellow. The optical density (OD) is measured spectrophotometric ally at a wavelength of 450 nm ± 2 nm. The OD value is proportional to the concentration of

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Human AGER. You can calculate the concentration of Human AGER in the samples by comparing the OD of the samples to the standard curve.

Statistical Analysis:

Statistical analysis was carried out using SPSS version 23. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (Means ± SD). Student t-test was used to compare means between two groups. ANOVA test was used to compare means between three groups or more. Mann-Whitney test was used to compare means between two groups when variable was not normally distributed. Chi-square test was used to find the association between categorical variables. Correlation coefficient (r) was used to assess the relationship between two continuous variables. A *p*-value of ≤ 0.05 was considered as significant.

Results

Demographic data of the study patients

Table (1) show the demographic characteristics of patients in both studied group. The mean age of all patients in our study was 56.13 ±8.60 years; there were no significant differences in the mean age between both groups (P > 0.05)

Statistical analysis showed the were no significant differences regarding gender, smoking and residence between both studied group (group I and II). (P > 0.05)

The only statistically significant finding in demographic data between both group was the presence of family history of diabetes (P < 0.05).

Table (1) Demographic data of the study patients

Study variables	Group I (N=91)	Group II (N=58)	Total (N=149)	P-value
Age (years)	56.67 ± 8.79	55.29 ± 8.31	56.13 ± 8.60	0.343
Gender				0.715
Male	49 (53.8)	33 (56.9)	82 (55.0)	
Female	42 (46.2)	25 (43.1)	67 (45.0)	
Total	91 (100.0)	58 (100.0)	149 (100.0)	
Smoking				0.699
Yes	18 (19.8)	13 (22.4)	31 (20.8)	
No	73 (80.2)	45 (77.6)	118 (79.2)	
Total	91 (100.0)	58 (100.0)	149 (100.0)	
Residence				0.291
Urban	60 (65.9)	43 (74.1)	103 (69.1)	
Rural	31 (34.1)	15 (25.9)	46 (30.9)	
Total	91 (100.0)	58 (100.0)	149 (100.0)	

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Family history				
Yes	63 (69.2)	30 (51.7)	93 (62.4)	0.031*
No	28 (30.8)	28 (48.3)	56 (37.6)	
Total	91 (100.0)	58 (100.0)	149 (100.0)	

* Significant differences at P≤0.05

Group I = Patients with diabetic neuropathy.

Group II = Patients without diabetic neuropathy.

Basal characteristics of all patients in the study

Table (2) shows non-significant difference in the duration of diabetes between patients with diabetic neuropathy in comparison withpatients without diabetic neuropathy.(P < 0.06)

There was highly significant difference in the HbA1C level between patients with diabetic neuropathy in comparison with patients without diabetic neuropathy (P < 0.01).

There was non-significant difference in the body mass index (BMI) between patients with diabetic neuropathy in comparison withpatients without diabetic neuropathy (P > 0.05)

Regarding other complications of diabetes, the study found that although there were no significant differences between both group regarding hypertension and diabetic nephropathy (p. > 0.05), however there was highly significant difference in diabetic retinopathy between patients with diabetic neuropathy andpatients without diabetic neuropathy (p. < 0.01). Table 2

Table (2) Basal characteristics of all patients in the study

Study variables	Group I (N=91)	Group II (N=58)	Total (N=149)	P-value
Duration (years)	11.73 ± 7.39	10.60 ± 5.07	10.90 ± 6.65	0.06
BMI (Kg/m^2)	29.09 ± 2.66	29.07 ± 2.64	29.08 ± 2.65	0.966
HbA1C	8.15 ± 1.37	7.27 ± 1.24	7.80 ± 1.39	<0.001**
Hypertension				
Yes	60 (65.9)	43 (74.1)	103 (69.1)	0.291
No	31 (34.1)	15 (25.9)	46 (30.9)	
Total	91 (100.0)	58 (100.0)	149 (100.0)	
Diabetic retinopathy				
Yes	76 (83.5)	10 (17.24)	86 (57.7)	0.005**
No	15 (16.5)	48 (82.76)	63 (42.3)	
Total	91 (100.0)	58 (100.0)	149 (100.0)	
Diabetic nephropathy				
Yes	5 (5.5)	1 (1.7)	6 (4.0)	0.405
No	86 (94.5)	57 (98.3)	143 (96.0)	
Total	91 (100.0)	58 (100.0)	149 (100.0)	

** highly significant differences at P≤0.01

Group I=- Patients with diabetic neuropathy.

Group II = Patients without diabetic neuropathy.

Distribution of patients with diabetic neuropathy according to severity

Figure (1) shows that the majority (51.6%) of patients presented with moderate diabetic neuropathy, severe diabetic neuropathy presents in 29.75 % of patients while only 18.7% of patients presents with mild form of diabetic neuropathy.

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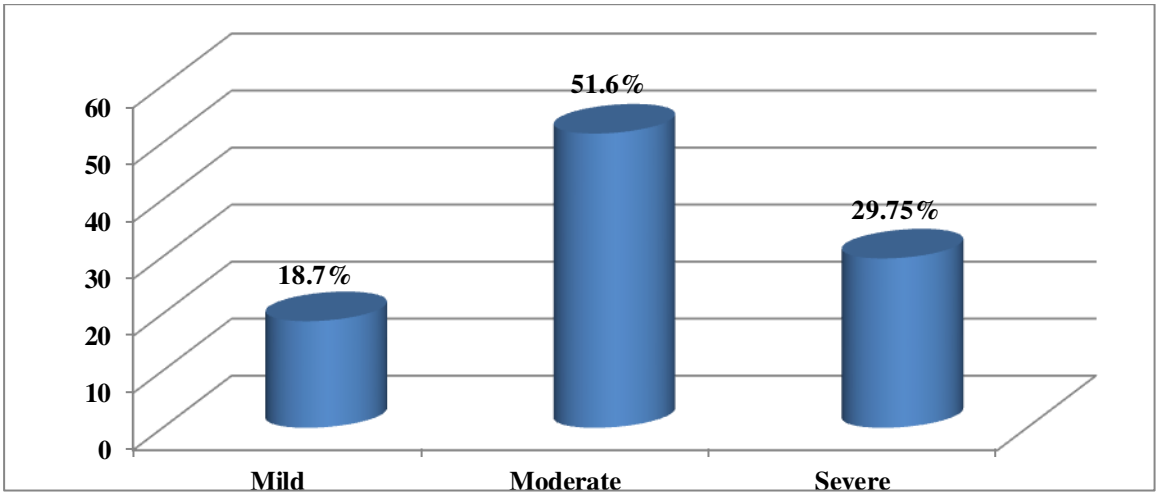

Figure(1) Distribution of patients with diabetic neuropathy according to severity.

The correlation between AGE and different patients parameters.

Figure (2) shows that although the level of Advanced glycation end products increases with increasing patients age however the correlation is statistically insignificant. (N=149, r=0.158, P=0.054).

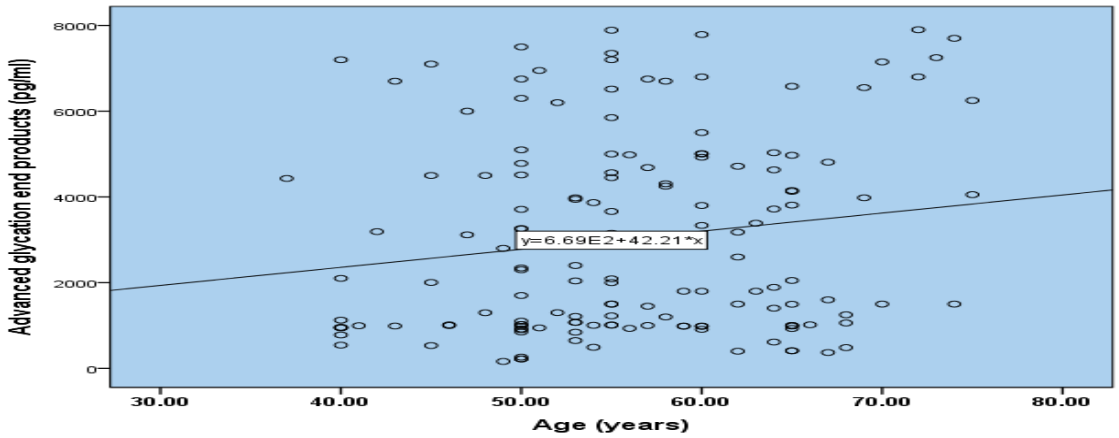

Figure (2)The correlation between patients age and Advanced glycation end products.

Figure (3) shows that there was statistically significant positive correlation between BMI and Advanced glycation end products among diabetic patients. **(N=149, r=0.19, P=0.02).**

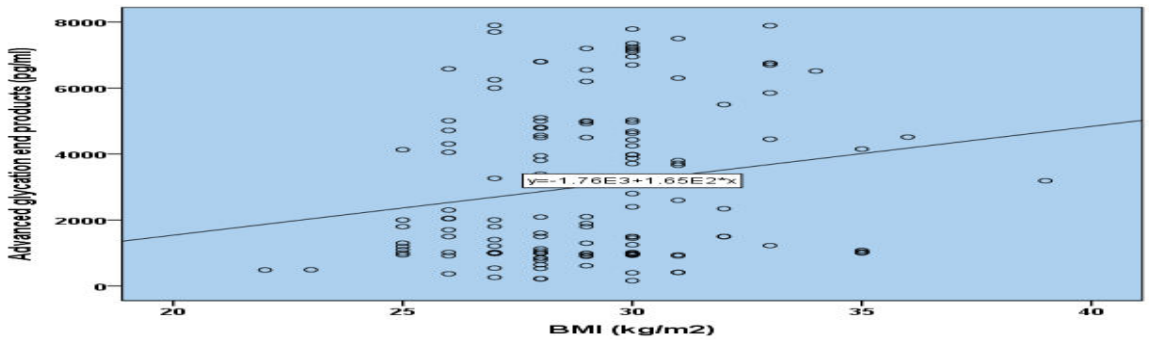

Figure (3) The correlation between BMI (kg/m^2) and Advanced glycation end products.

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Figure (4) shows that there ishighly significant positive correlation between duration of disease and Advanced glycation end products among diabetic patients. **(N=149, r=0.383, P. <0.001**).**

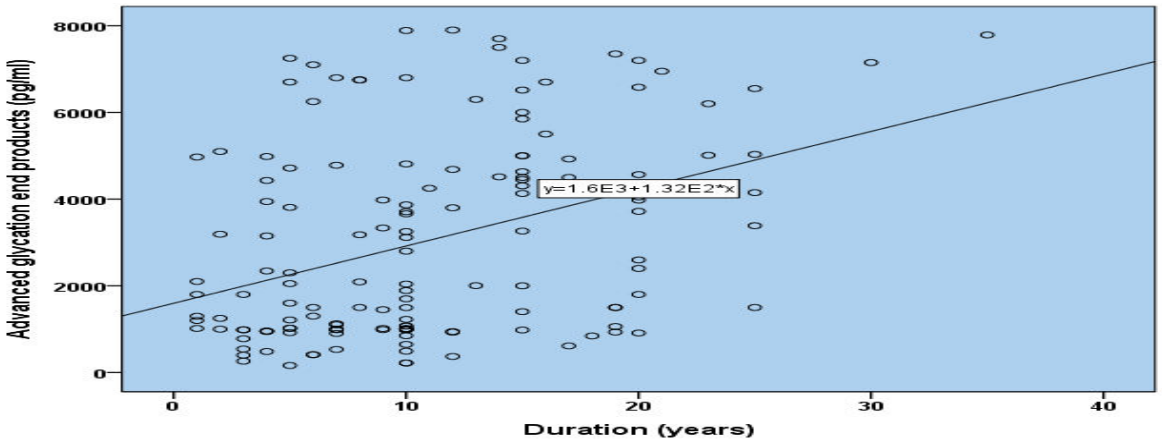

Figure (4) The correlation between duration of disease and advanced glycation end products.

** Highly significant differences at P≤0.01.

The correlation between RAGE and different patients' parameters

Figure (5) shows that there was no statistically significant correlation between patients age and Receptor of Advanced glycation end products among diabetic patients. (N=149, r=0.152, P=0.064).

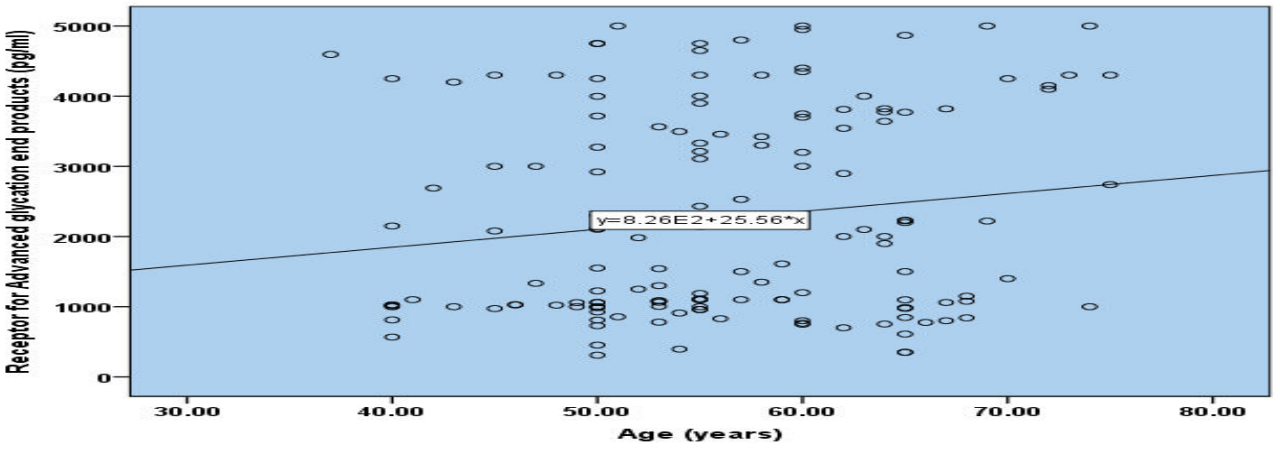

Figure (5) The correlation between patients age and Receptor of advanced glycation end products

Figure (6) shows that there was statistically significant positive correlation between BMI and Receptor of Advanced glycation end products among diabetic patients. **(N=149, r=0.199, P=0.015*).**

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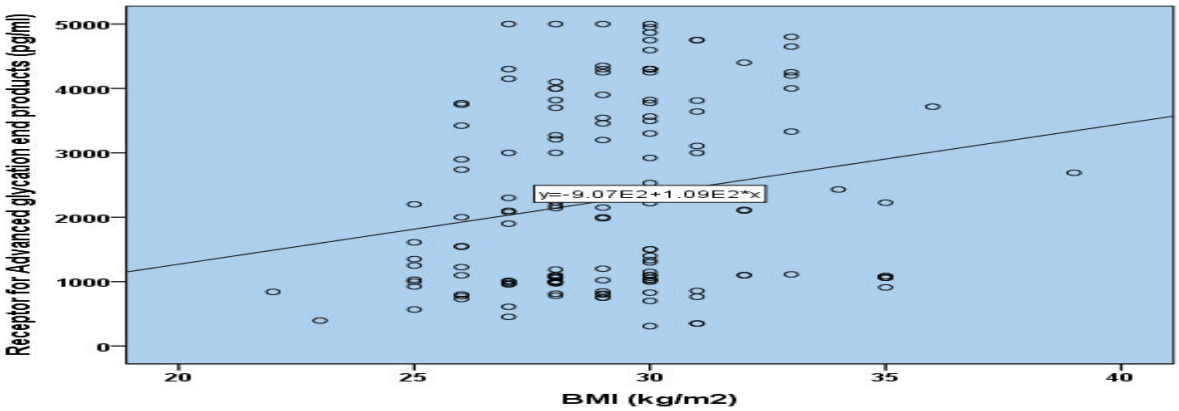

Figure(6) The correlation between BMI and Receptor of advanced glycation end products.

* highly significant differences at P≤0.05

Figure (7) shows that there was highly significant positive correlation between duration of disease and receptor of advanced glycation end products among diabetic patients. **(N=149, r=0.359, P=<0.001**).**

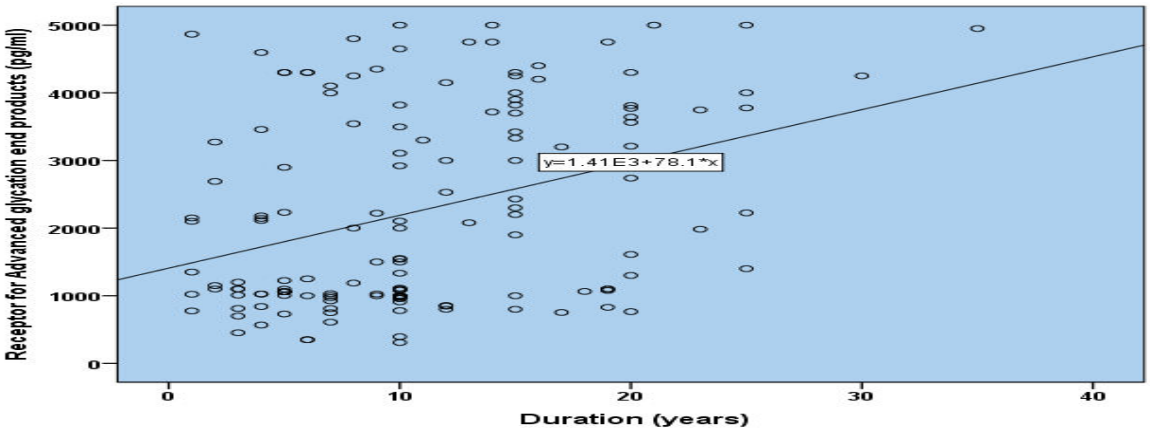

Figure (7) The correlation between duration of disease and Receptors of advanced glycation end products.

** Highly significant differences at P≤0.01

Advanced glycation end products (AGE) and Receptor for Advanced glycation end products (RAGE) level according to study groups.

Table (3) shows that the mean of the level Advanced glycation end products (AGE) and Receptor for Advanced glycation end products (RAGE) was significantly higher patients with diabetic neuropathy in comparison withpatients without diabetic neuropathy. (p. < 0.01).

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Table (3) Advanced glycation end products (AGE) and Receptor for Advanced glycation end products (RAGE) level according to study groups.

Study variables	Study group	N	Mean ± SD	t-test	P-value
AGE. (pg/ml)	I	91	4146.86±2171.87	10.56	<0.001**
	II	58	1299.78±1098.33		
RAGE. (pg/ml)	I	91	2945.12±1378.08	10.17	<0.001**
	II	58	1185.47±724.79		

** highly significant differences at P≤0.01

Group I = Patients with diabetic neuropathy.

Group II = Patients without diabetic neuropathy.

AGE: Advanced glycation end products, RAGE: Receptor for Advanced glycation end products.

Advanced glycation end products and its receptors according to severity of diabetic neuropathy

Table (4) shows that the serum level of advanced glycation end products and receptors for advanced glycation end products constantly increased with the severity of diabetic peripheral neuropathy.

Table(4) Advanced glycation end products and its receptors according to severity of diabetic neuropathy

Study variables	Severity	N	Mean	SD	F-test	P-value
AGE (pg/ml)	Mild	17	1778.24	478.38	28.34	<0.001**
	Moderate	47	4073.85	1573.95		
	Severe	27	5765.30	2325.17		
RAGE (pg/ml)	Mild	17	1448.88	390.38	24.09	<0.001**
	Moderate	47	2963.00	1121.21		
	Severe	27	3856.07	1389.18		

** highly significant differences at P≤0.01

Group I = Patients with diabetic neuropathy.

Group II = Patients without diabetic neuropathy.

AGE: Advanced glycation end products, RAGE: Receptor for Advanced glycation end products.

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Discussion

During the past few years it has become evident that AGE/RAGE axis is involved in a plethora of pathophysiologically relevant conditions ranging from complications of diabetes and amyloidosis to inflammatory responses and cancer[10].However, the roles of AGE/RAGE axis in the function of nervous system have been studied to a lesser extent. It is known that RAGE mediates neurite outgrowth and promotes cell survival upon binding to its ligands amphoterin and members of the S100 protein family [11,12].The present study found that although the level of AGE and RAGE increase with patients age however the relation was statistically insignificant.Uribarri J and co-workers in 2007 investigated whether AGEs intake correlated with glycotoxin levels, markers of inflammation and oxidative stress (OS) comparing older versus younger healthy adults. They studied 172 healthy volunteers in two groups (18–45 years) and (60–80 years). The CML and MG derivatives were higher in the older group[13].Vlassara H and his associates in 2009found similar results in a study with 325 healthy participants and 66 participants with kidney disease (CKD)[14]. The present study found that there was statistically significant positive correlation between BMI and Advanced glycation end products (**P=0.02**) and receptors for Advanced glycation end products (**P=0.015)** among all diabetic patients (with and without neuropathy). Yamagishi *et al*., 2006 and Nakamura *et al*., 2008 have demonstrated that AGEs are markedly elevated within type 2 diabetic patients and/ or illustrated a strong positive correlation between AGEs and BMI[15,16].
He *et al*., in 2014demonstrate that BMI was an independent predictive factor for plasma sRAGE levels in adolescents[17].In contrast to our results, Rowisha and his associates in 2016found that adolescents with obesity had reduced sRAGE[18].The explanation for the different results may be related to the type of patients, as most of our patients is older than 50 years, in addition all our patients were diabetic while that study done on obese adolescent subjects. Our study shows that there ishighly significant positive correlation between duration of disease and AGE and RAGE among diabetic patients.The present study found that the mean level of advanced glycation end products (AGE) was 4146.86±2171.87 pg/mlin group I which was significantly higher than its level in group II 1299.78±1098.33 pg/ml. The mean level of receptor for advance glycation ends products (RAGE) was 2945.12±1378.08 pg/mlin group I which was significantly higher than its level in group II 1185.47±724.79 pg/ml.Gohda T and coworkers in 2008 their results were consistent with our results they found a significant higher serum AGE level in T2DM patients having microvascular complications and concluded that AGE level has been suggested to act as a predictor of cardiovascular disease mortality and diabetic nephropathy[19].

In diabetes, AGE accumulation may result from chronichyperglycemia promoting the generation of AGEs, and also with concomitant impairedrenal function because the kidney is the major site of AGE clearance. AGE modified proteins may be more resistant to enzymatic degradation and it is likely that this further promotes local tissue AGE accumulation[20].

The effects of AGEs may be classified as receptor-independent or -dependent, and can act intracellular or circulate and act on cell surface receptors such as the receptor for AGEs

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(RAGEs). Advanced glycation occurs over a prolonged period, affecting long lived proteins. The structural components of the connective tissue matrix and, in particular, basement membrane components such as type IV collagen are prime targets, but other long-lived proteins can also undergo advanced glycation, including myelin, tubulin, plasminogen activator 1, and fibrinogen [21].Extracellular matrix (ECM) proteins are susceptible to AGE modification because of their slow turnover rate. The formation of intermolecular and intermolecular crosslinks with collagen as a result of the glycation process leads to structural alterations, leading to increased stiffness and resistance to proteolytic digestion [22].

The present study also found that the receptors for advance glycation end products were also significantly higher in patients with DPN compared to patients without DPN. This result is consistent with the result of another study which found that activation of RAGE by AGEs and other ligands has been suggested to be an important mediator of vascular complications in diabetes [23]. Another study found that the circulating levels of sRAGE are increased in individuals with diabetes, especially those with microvascular and/or macro vascular complications of their disease [24]. Auberta nd coworkers in 2014 conducted a study on 198 T2DM individuals, the study concluded that RAGE level was associated with DPN in individuals with T2DM. this confirms the relationship between advanced glycation and DPN independent on other risk factors[25].

The present study found that the serum level of advanced glycation end products and receptors for advanced glycation end products constantly and significantly increase with the severity of diabetic peripheral neuropathy. In present study we found that the mean level of advanced glycation end products was (1778.24),(4073.85) and (5765.30) in mild, moderate and severe DPN respectively,meanwhile the mean level of their receptors were(1448.88) in mild cases, (2963.00) in moderate cases and (3856.07) in severe cases. This Showing that the serum level of advanced glycation end products and receptors for advanced glycation end products constantly increased with the severity of diabetic peripheral neuropathy and this statically highly significant difference among them P≤0.01 Although many studies like Gohda *et al*.,2008 and Aubert *et al*., 2014 found strong relation between AGE and RAGE and diabetic neuropathy however there is no study has linked the score of neuropathy (mild, moderate, and severe) with the level of AGE and RAGE. In present study we found a relation of AGE &RAGE level significantly associated with severity of DPN using Toronto clinical scoring system.

Conclusions

There is significant positive association between AGE & RAGE with occurrence and severity of diabetic peripheral neuropathy.

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