Study of advanced glycation endproducts and their receptors in Egyptian type 2 diabetic individuals with peripheral neuropathy

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Context
Diabetic neuropathy is one of the commonest long-term complications of diabetes seen in routine healthcare and considered the most common cause of peripheral neuropathy in developed world.
Aim
The aim of our work was to measure advanced glycation endproducts (AGEs) and their receptors (RAGEs) in diabetic peripheral neuropathy (DPN), both painful and painless DPN.
Patients and methods
Our study was conducted on 50 type 2 diabetes mellitus patients with peripheral neuropathy, divided into two subgroups: the first group included 25 patients with painful DPN and the second group included 25 patients with painless DPN. Moreover, a third group included 20 diabetic patients without peripheral neuropathy, and a fourth group that included 20 healthy participants. All groups were subjected to full history taking and clinical examination, anthropometric parameters, the calculation of neuropathy disability score, and nerve conduction studies (peroneal, sural, and tibial nerves). Laboratory investigations included serum AGEs and RAGEs.
Results
Our study demonstrated that hemoglobin A1c, AGE, and RAGE showed statistically significant difference between the studied groups. Hemoglobin A1c was significantly high in both neuropathic and diabetic groups in comparison with control. Regarding AGE, it was statistically higher in neuropathic group than in control ($P<0.011$). On the contrary, RAGE was significantly higher in both neuropathic and diabetic groups rather than control ($P<0.02$). Although the neuropathic group has higher levels of AGE and RAGE than diabetic group, the difference was statistically nonsignificant. Significant difference was found between studied groups regarding nerve conduction studies of sural and tibial nerves. Statistically significant difference was found in the parameters of nerve conduction studies between neuropathic group and both non-neuropathic diabetic and control groups.
Conclusion
Our study concluded that AGE and RAGE are significantly higher in diabetic patients with neuropathy versus control, with more elevation in neuropathic group than in diabetic without neuropathy.

Keywords:
advanced glycation endproduct, diabetes, diabetic peripheral neuropathy, receptor for advanced glycation endproduct

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Introduction

Diabetes has been associated with different long-term macrovascular and microvascular complications. The macrovascular involves large vessels causing peripheral vascular disease, cardiovascular disease, and cerebrovascular disease. Microvascular complications include neuropathy, retinopathy, and nephropathy [1]. Diabetic peripheral neuropathy (DPN) was recognized by the American Diabetes Association as 'the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes' [2]. Long-term complications of diabetes have long been believed to be the result of prolonged hyperglycemia. However, blood glucose levels alone do not reveal the whole picture. Diabetic neuropathy is one of the commonest complications of diabetes, reaching

37.4% among uncontrolled diabetic individuals. In the USA, 11.9 million adults have been diagnosed as having diabetes, and of these, 3.9 million (32.7%) have DPN [3]. Painful DPN were found in ~11% of all diabetic individuals [4]. A diabetic complications study by Herman *et al.* [5] in Egypt, which used the vibration perception threshold to define DPN, demonstrated that 22 and 18% of known and newly diagnosed diabetic individuals, respectively, had DPN. One study based on clinical neuropathic symptoms and nerve conduction studies (NCSs) found that 8.3% of 86 patients with newly diagnosed type 2 diabetes mellitus (T2DM) had DPN [6]. Using the diabetic neuropathy score and diabetic neuropathy examination score to define DPN in their study in the United Arab Emirates, Saadi *et al.* [7] demonstrated that 34.7% among 57 diabetic individuals had DPN.

Studies have shown that those who have higher levels of advanced glycation endproducts (AGEs) experience more microvascular and cardiovascular complications [8]. AGEs are groups of compounds that result from the nonenzymatic reaction of reducing sugars with free amino groups of biological molecules. Receptors of advanced glycation endproducts (RAGEs), which are signal transduction receptors that belong to the immunoglobulin superfamily, are expressed in a variety of cell types, such as neurons, monocytes, smooth muscle cells, lymphocytes, and endothelial cells [9]. The interaction between AGE and RAGEs leads to intracellular production of reactive oxygen species through electron transport chain, xanthine oxidase, NADPH oxidase, and arachidonic acid metabolism [10,11]. AGEs detect the modification of myelin of the peripheral nerve, which becomes susceptible to phagocytosis, and determine segmental demyelination. Also AGEs responsible for modification of major axonal cytoskeleton proteins (e.g. actin, tubulin, and neurofilament), which cause atrophy of axon and impairment of axonal transport [12]. Study of AGEs represent one of the most promising areas of research, as it is thought to have an important role in the etiology of complications of diabetes mellitus (DM), and this will provide new possible targets for the management of both type 1 DM and T2DM and related complications [13].

The aim of our work was to measure AGEs and RAGEs in DPN, both painful and painless DPN.

Patients and methods

Our study is a cross-sectional study, which was carried out in outpatient clinic and inpatient ward of specialized Internal Medical Hospital, Mansoura University. The study was approved by the Mansoura Faculty of medicine, ethics committee, and then it has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. A written informed consent was obtained from all participants before inclusion in the study.

Timing of the study

The study period was of 1 year between December 2014 and December 2015.

Groups of the study

The patients were divided into the following groups: neuropathic group had 50 T2DM patients with DPN and was divided into two subgroups: the first group included 25 patients with painful DPN and the second group included 25 patients with painless DPN. The third group included 20 diabetic patients without peripheral nerve dysfunction. The fourth group included 20 healthy individuals as controls from medical staff, with matched age and sex.

Exclusion criteria

Patients who refused to participate in the study, patients who had type 1 DM, patients with serum creatinine level more than 1.5 mg/dl, patients with long-term liver disease, patients with other causes of neuropathy, patients with severe debilitating diseases, pregnant females, those with other malignancies, and patients on chemotherapy or radiotherapy.

Methodology

Clinical assessment

It included full history taking and thorough clinical examination, anthropometric parameters (BMI and waist circumference), the calculation of neuropathy disability score [14], and presence or absence of deep tendon reflexes and sensation (graded as 0, normal; 1, positive with reinforcement; 2, absent). Vibration perception threshold was tested with tuning fork 128 Hz on each malleolus, pain sensation by pin prick, temperature sensation by thermal pen, assessment of pain by visual analog pain scale.

Laboratory investigations

Laboratory investigations included urine analysis. Microalbumin level was assayed using competitive

enzyme-linked immunosorbent assay (ELISA) test system for the quantitative measurement of human albumin level in urine, which was supplied by ORGENTEC Diagnostic GmbH (Mainz, Germany). Conventional laboratory tests included serum glucose and creatinine levels. Serum AGE was assayed by solid-phase sandwich ELISA assay, which was supplied by MyBiosowle (catalog number: MBS 704358), whereas RAGE was assayed by solidphase ELISA using Quanitikine RAGE ELISA Kit, which was supplied by R&D System (catalog number: DRG00). Serum of 1 ml was put into EDTA vacutainer tube for hemoglobin A1c (HbA1c) assay using fast cation exchange resin, which was supplied by Human Gesellschaft für Biochemica und Diagnostica mbH (Wiesbaden, Germany).

Nerve conduction studies

studies NCSs were performed with the use of sensory nerve to record the conduction velocity for peroneal nerve, sural nerve, and tibial nerve. DPN was diagnosed by NCSs and neuropathy disability score. Patients with DPN were divided by visual analog scale for pain into painful and painless groups.

Fundus examination

Fundus examination was done by digital retinal camera [15].

Results

The results are shown in Tables 1–11.

Table 1 Comparison between different studied groups according to demographic characteristics

Groups	*N*	Mean	SD	Significance
Age				
Diabetic	20	57.8000	6.36272	0.39
Control	20	53.8500	6.40127	
Neuropathic	50	57.8200	5.73457	

Groups	Male (%)	Female (%)	Significance
Sex			
Diabetic	60	40	0.523
Control	65	35	
Neuropathic	66	34	

Groups	*N*	Mean	SD	Significance
Comorbidity (hypertension and ischemic heart disease)				
Diabetic	20	1.50	0.688	0.020
Control	20	2.95	4.501	
Neuropathic	50	1.32	0.713	

Table 2 Comparison between painful and painless groups according to demographic characteristics

Groups	*N*	Mean	SD	Significance
Age				
Painful	25	56.8400	5.92087	0.231
Painless	25	58.8000	5.48483	
Sex				
Painful	25	2.1600	2.70308	0.133
Painless	25	1.3200	0.47610	
Duration of diabetes mellitus				
Painful	25	0.00	0.00	
Painless	25	0.00	0.00	
Medication				
Painful	25	1.8400	0.37417	0.270
Painless	25	1.8000	0.40825	
Comorbidity				
Painful	25	1.32	0.690	1.000
Painless	25	1.32	0.748	

Painful and painless groups did not show statistically significant difference in age, sex, medication, and comorbidity.

Table 3 Comparison between painful and painless groups according to glycated products

Groups	*N*	Mean	SD	Significance
HbA1c				
Diabetic	20	9.1050	1.30120	0.000
Control	20	5.3950	0.50729	
Neuropathic	50	9.1260	1.75567	
AGE				
Diabetic	20	1483.9500	703.70280	0.030
Control	20	1252.5500	324.97489	
Neuropathic	50	1780.8400	905.55881	
RAGE				
Diabetic	20	1322.8500	348.20552	0.032
Control	20	1272.9500	273.56121	
Neuropathic	50	1537.7600	497.33890	

HbA1c, AGE, and RAGE showed statistically significant difference between studied groups. AGE, advanced glycation endproduct; HbA1c, hemoglobin A1c; RAGE, receptor for advanced glycation endproduct.

Table 4 Comparison between painful and painless groups according to glycated products and receptor for advanced glycation endproduct

	N	Mean	SD	Significance
HbA1c				
Painful	25	9.2440	1.69167	0.639
Painless	25	9.0080	1.84457	
AGE				
Painful	25	1643.7200	1040.28860	0.289
Painless	25	1917.9600	743.55276	
RAGE				
Painful	25	1523.0400	547.35200	0.837
Painless	25	1552.4800	452.71672	

Painful and painless groups showed no statistically significant difference concerning glycated products. AGE, advanced glycation endproduct; HbA1c, hemoglobin A1c; RAGE, receptor for advanced glycation endproduct.

Table 5 Comparison between different studied groups according to nerve conduction on sural, peroneal, and tibial nerves

	Sural				Peroneal				Tibial			
	N	Mean	SD	Significance	*N*	Mean	SD	Significance	*N*	Mean	SD	Significance
Amplitude												
Diabetic	20	10.800	0.6513	0.000	20	3.175	0.5600	0.000	20	3.730	0.4835	0.000
Control	20	11.365	0.9287		20	3.395	0.8835		20	4.865	1.1717	
Neuropathic	50	6.422	2.9400		50	1.484	0.2860		50	2.646	0.3045	
Latency												
Diabetic	20	3.115	0.4648	0.000	20	4.570	0.9348	0.000	20	4.655	0.7612	0.000
Control	20	3.105	0.5472		20	4.250	0.7409		20	4.330	0.5079	
Neuropathic	50	4.784	1.9157		50	5.638	0.3301		50	4.978	0.5320	
Velocity												
Diabetic	20	48.650	5.1736	0.000	20	50.700	5.6298	0.000	20	51.150	5.6127	0.000
Control	20	50.550	4.8065		20	51.450	5.0936		20	52.200	4.5259	
Neuropathic	50	31.660	11.9840		50	36.900	1.8434		50	36.640	2.3366	

Significant difference was found between studied groups regarding nerve conduction studies on sural, peroneal, and tibial nerves. Statistically significant difference was found in the parameters of nerve conduction studies between neuropathic group and both non-neuropathic and control groups.

Table 6 Comparison between painful and painless groups according to nerve conduction studies on sural, peroneal, and tibial

	Peroneal patients				Sural patients				Tibial patients			
	N	Mean	SD	Significance	*N*	Mean	SD	Significance	*N*	Mean	SD	Significance
Amplitude												
Painful	25	1.476	0.2876	0.846	25	6.352	3.0277	0.868	25	2.568	0.3211	0.070
Painless	25	1.492	0.2900		25	6.492	2.9105		25	2.724	0.2712	
Latency												
Painful	25	5.692	0.3378	0.251	25	4.636	1.8421	0.590	25	4.960	0.6042	0.814
Painless	25	5.584	0.3197		25	4.932	2.0134		25	4.996	0.4605	
Velocity												
Painful	25	37.040	2.1111	0.596	25	32.200	12.2916	0.754	25	36.240	2.3678	0.230
Painless	25	36.760	1.5620		25	31.120	11.8965		25	37.040	2.2818	

No statistically significant difference was found in the parameters between painful and painless groups regarding peroneal, sural, and tibial nerves.

Table 7 Correlation of advanced glycation endproduct and different studied variables in diabetic group

	R	Significance
AGE		
HbA1c	0.018	0.987
Age	–1.263	0.334
Medication	–0.837	0.491
Comorbidity	0.980	0.430
Cholesterol	0.006	0.996
TG	–0.138	0.903
LDL	–0.005	0.996
HDL	–0.119	0.916
Diabetic (sural)		
Amplitude	0.079	0.944
Latency	1.923	0.194
Velocity	–1.200	0.353
Diabetic (peroneal)		
Amplitude	–0.166	0.883
Latency	–0.778	0.518
Velocity	0.544	0.641
Diabetic (tibial)		
Amplitude	1.474	0.278
Latency	0.039	0.972
Velocity	1.825	0.210

AGE, advanced glycation endproduct; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 8 Correlation of advanced glycation endproduct and different studied variables in control group

	R	Significance
AGE		
HbA1c	–0.701	0.488
Age	–0.021	0.984
Medication	0.330	0.743
Comorbidity	1.099	0.280
TG	0.060	0.953
LDL	–1.041	0.305
HDL	0.506	0.616
Neuropathic (sural)		
Amplitude	–0.519	0.607
Latency	–0.652	0.519
Velocity	1.139	0.263
Neuropathic (peroneal)		
Amplitude	–1.070	0.292
Latency	–0.884	0.383
Velocity	0.106	0.916
Neuropathic (tibial)		
Amplitude	–0.443	0.660
Latency	–1.509	0.141
Velocity	–1.359	0.183

AGE, advanced glycation endproduct; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride.

Table 9 Correlation of advanced glycation endproduct and different studied variables in neuropathic group

	R	Significance
AGE		
HbA1c	2.363	0.099
Age	–2.631	0.078
Comorbidity	–0.341	0.756
Cholesterol	–0.542	0.625
TG	0.117	0.914
LDL	0.645	0.565
HDL	–0.928	0.422
Control (sural)		
Amplitude	–1.316	0.280
Latency	1.621	0.203
Velocity	–1.508	0.229
Control (peroneal)		
Amplitude	–1.882	0.156
Latency	–0.593	0.595
Velocity	–1.343	0.272
Control (tibial)		
Amplitude	1.603	0.207
Latency	2.005	0.139
Velocity	0.912	0.429

There was no significant correlation between AGE and all variables studied in neuropathic, diabetic, and control groups. AGE, advanced glycation endproduct; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride.

Table 10 Correlation of receptor for advanced glycation endproduct and different studied variables in diabetic group

	R	Significance
RAGE		
HbA1c	0.866	0.478
Age	1.155	0.368
Medication	–0.364	0.751
Comorbidity	0.433	0.707
Cholesterol	–0.341	0.766
TG	0.057	0.960
LDL	0.291	0.798
HDL	0.237	0.835
Diabetic(sural)		
Amplitude	0.470	0.684
Latency	0.527	0.651
Velocity	–2.982	0.096
Diabetic (peroneal)		
Amplitude	0.248	0.827
Latency	0.743	0.535
Velocity	0.397	0.730
Diabetic (tibial)		
Amplitude	0.815	0.501
Latency	–1.022	0.414
Velocity	–1.673	0.236

HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RAGE, receptor for advanced glycation endproduct; TG, triglyceride.

Table 11 Correlation of receptor for advanced glycation endproduct and different studied variables in control and neuropathic groups

	Control group		Neuropathic group	
	R	Significance	*R*	Significance
RAGE				
HbA1c	0.087	0.936	0.331	0.743
Age	0.004	0.997	–0.197	0.845
Comorbidity	–1.295	0.286	0.382	0.705
Cholesterol	–1.391	0.258	2.139	0.040
TG	1.374	0.263	0.811	0.423
LDL	1.327	0.277	–1.139	0.263
HDL	0.584	0.600	–0.973	0.338
Sural				
Amplitude	1.087	0.357	–1.025	0.313
Latency	–0.468	0.672	–1.239	0.224
Velocity	–1.181	0.323	1.914	0.064
Peroneal				
Amplitude	–0.132	0.903	–1.203	0.238
Latency	1.177	0.324	–0.093	0.926
Velocity	–1.720	0.184	0.312	0.757
Tibial				
Amplitude	1.849	0.162	–0.238	0.814
Latency	1.554	0.218	–0.314	0.755
Velocity	1.645	0.199	–1.366	0.181

There was no significant correlation between RAGE and all variables studied in neuropathic, diabetic, and control groups. HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RAGE, receptor for advanced glycation endproduct; TG, triglyceride.

Discussion

Diabetic neuropathy is one of the commonest long-term complications seen in routine healthcare and considered the most common cause of peripheral neuropathy in developed countries [16]. It is, therefore, a major health problem with serious consequences for patients, and it results in a significant financial burden on the healthcare systems. This is especially true owing to the current global epidemic of DM. Hyperglycemia induces microvascular damage through different mechanisms: an increased flux of glucose and other sugars through the polyol pathway; an increased intracellular AGE formation; interaction between AGEs and RAGEs, leading to intracellular signaling, which disrupts cell function; a persistent activation of protein kinase C isoforms; and an increased hexosamine pathway activity. Selectively inhibiting each of these biochemical pathways has produced disappointing results [17]. Of particular interest is the accelerated formation of AGEs and their interaction with their receptors, RAGEs. The most important process responsible for AGE accumulation in diabetic patients is the nonenzymatic glycation reaction, or Maillard reaction. This can be globally seen as a different process; the final stage of which comprises a complex series of oxidation, dehydration, and cyclization reactions, which give rise to endogenous AGEs, that is, thermodynamically unstable compounds that typically accumulate on proteins with a long half-life, though they have been shown to form on proteins with a

short half-life too, such as plasma proteins, lipoproteins, and intracellular proteins [18].

The other way in which these compounds accumulate in diabetic patients is through a defective renal excretion of AGEs, typical of diabetic nephropathy, because renal clearance is inversely related to plasma levels of AGEs. This gradually creates a vicious circle as the greater circulating pool of plasma AGEs in turn changes the shape and structure of many proteins at glomerular level (particularly type IV collagen and the mesangium), as well as interacting with specific receptors. These interactions are associated with a worsening chronic kidney disease and further impairment of glycoxidation product clearance [19]. Much attention has recently been paid to exogenous AGEs, harmful products of 'browning' (or the Maillard reaction) in different foods. Together with endogenous AGEs, these compounds form the majority of glycation free adducts, the greater proportion of circulating AGEs in diabetic and nondiabetic individuals. Among the various food processing methods, heating, sterilizing, and microwaves contribute to the generation of exogenous AGEs. Binding of AGEs to RAGEs has been suggested to contribute to the pathogenesis of diabetic vascular complications. Interaction of AGE with its receptor RAGE transduces multiple signals such as NADPH oxidase, mitogen-activated protein kinases, extracellular signal regulated kinases, and GTPase [20]. Activation of NADPH oxidase causes enhanced (reactive oxygen species) generation, which may lead to peroxidation and glycoxidation reactions that result in protein carbonyl formation, advanced oxidation protein product generation, and lipid peroxidation. These oxidative stress markers have been shown to be enhanced significantly in diabetic patients. Using pharmacological agents that are able to inhibit AGE formation and disrupt the RAGE-ligand axis either through downregulating membrane-bound RAGE or inducing the production of circulating RAGEs may be a possible means to decrease diabetic vascular complications [21].

This cross-sectional study was conducted at the inpatient and outpatient clinics of specialized medical hospital, Mansoura University, to asses AGEs and their receptors in both painful and painless DPN. The study comprised 50 patients with diabetic neuropathy (proved by NCSs); 25 patients had painful neuropathy, with 8% of patients showing marked degree of pain, whereas 8% showing least degree of pain. The other 25 patients had painless neuropathy. Moreover, there were 20 diabetic patients without neuropathy and 20 healthy individuals. All were enrolled by simple randomization.

Clinical data of our study revealed that there was no statistically significant difference between the different groups regarding age and sex. However, in all studied groups, the proportion of males was more than females (66 and 34%, respectively); this could be explained simply by refusal of females to do NCSs rather than increase prevalence of neuropathy in males. Hypertension and ischemic heart disease were significantly higher in the neuropathic group in comparison with the control group. This is shown in the study of comorbidity, with a significance of P value equal to 0.02. This may be because of high prevalence of dyslipidemia, hypertension, obesity, and other cardiovascular risk factors in diabetic patients. Ischemic heart disease is considered one of the most common causes of death in diabetic patients with peripheral neuropathy [22]. Painful and painless groups showed no statistically significant difference in age, sex, medication, and comorbidity.

The study of glycated products demonstrated that HbA1c was found to be significantly high in both neuropathic and diabetic groups versus control. Regarding AGE, it was statistically higher in neuropathic group compared with control ($P<0.011$). On the contrary, RAGE was significantly higher in both neuropathic and diabetic groups compared with the control group ($P<0.02$). Although the neuropathic group has higher level of AGE and RAGE than diabetic group, the difference was statistically nonsignificant. Our results are consistent with a study that showed a significant higher level of serum AGE level by ELISA in T2DM patients having microvascular complications. It showed that AGEs were ~23% higher in diabetic patients compared with healthy participants and concluded that AGE level has been suggested to act as a predictor of cardiovascular disease mortality and diabetic nephropathy [22]. This also correlates with another study that stated that presence of RAGE in blood was significantly higher in diabetic individuals than controls ($P<0.01$) [23]. Another research work obtained the same results with a significance of P value equal to 0.028. It concluded that RAGE was independently associated with DPN in individuals with T2DM in a study conducted on 198 T2DM individuals, confirming the relationship between advanced glycoxidation and DPN, independently of other risk factors [24]. Interference of exogenous AGE with the sensitivity of the assay could be the cause of making the difference nonsignificant between

neuropathic and diabetic groups in our study, so further studies should consider assessment of exogenous AGE. Correlations between AGE and RAGE and all other variables including age, sex, comorbidity, HbA1c, and parameters of NCS were done for our studied groups, but no statistically significant correlation was found. NCSs can diagnose diabetic neuropathy at a very early stage even before symptoms and signs set in, as demonstrated from a study conducted on 50 diabetic patients and 50 nondiabetic controls of comparable age and BMI [25]. This goes with our study where there was a statistically significant difference in all categories of nerve conduction regarding sural, tibial, and peroneal nerves between neuropathic group and both diabetic and control groups. Painful and painless groups did not show statistically significant difference regarding glycation endproducts and all parameters of NCS. The distinction between painful and painless neuropathy is not clear in the literature. In this study, we tried to study some of the pathogenetic mechanisms of diabetic neuropathy to accuse AGEs and their receptors as one of these mechanisms.

Conclusion

Our study concluded that AGE and RAGE are significantly higher in diabetic patients with neuropathy versus control. Although the neuropathic group has higher level of AGE and RAGE than diabetic group, the difference was statistically nonsignificant, so further studies are suggested to exclude conflicting agents.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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