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THE RELATIONSHIP BETWEEN ADVANCED GLYCATION END PRODUCTS AND CORONARY RISKS, ABDOMINAL AORTIC DIAMETER AND PERIPHERAL ARTERIAL DISEASE AMONG ELDERLY DIABETICS

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Keywords:

Advanced glycation end products, Elderly diabetics, coronary risks, abdominal aorta, peripheral arterial disease.

Abstract

BACKGROUND AND OBJECTIVES: In elderly diabetic patients, DM is associated with accelerated complications and exaggerated functional deterioration. It is known that AGEs are associated with predisposition to diabetic complications, however studying the effect of AGEs in elderly population with multiple comorbid diseases is little. The purpose of the study was to detect the relationship between advanced glycation end products and coronary risk factors, abdominal aortic diameter and peripheral arterial disease in elderly diabetics.

SUBJECTS AND METHODS: case control study enrolled ninety elderly subjects who were divided into 3 groups thirty elderly diabetic subjects with comorbid diseases, thirty elderly diabetic subjects without comorbid diseases, and thirty healthy elderly subjects without diabetes as the control group. Each subject measured total AGEs level, abdominal aortic diameter at the level of iliac bifurcation, and ABI with hand held doppler.

RESULTS : AGEs were higher in the control group than other groups, no significant correlation was found between AGEs and abdominal aortic diameter, and there was inverse correlation between AGEs and ABI among group with DM only.

CONCLUSION: the use of plasma levels of AGEs as biomarkers for increased CVD risk in elderly may be limited and therefore alternative measurements of AGEs burden should be considered.

Introduction

In old age (≥60 years old), DM is becoming an alarming public health problem, as for some authors one from two old persons are diabetic or prediabetic and for others 8 from 10 old persons have some dysglycemia.[1] Moreover its prevalence and its co-morbidities and mortality are higher in elderly than in young people.[2]Elevated levels of circulating advanced glycation end products (AGEs) in the presence of hyperglycemia are believed to play a major role in the pathogenesis of macro-vascular and micro-vascular diseases observed in diabetes mellitus[3]. AGEs are believed to have a key role in the development and progression of cardiovascular disease in patients with DM[4]. Patients with type 2 diabetes have a high risk for early and extensive development of peripheral arterial disease (PAD) and this excess risk is not explained by increased burden of traditional atherosclerotic risk factors[5].Activation

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of the receptor for advanced glycation end products (RAGE) could be one additional mechanism for accelerated PAD and increased risk for amputation and death[5]. The binding of RAGE to its ligands induces cytokine production and inflammatory reactions, all of which are involved in the development and progression of AAAs[6].Data on AGEs in elderly population with multiple comorbid diseases is little. Hence the purpose of the study was to detect the relationship between advanced glycation end products and coronary risk factors, abdominal aortic diameter and peripheral arterial disease in elderly diabetics.

Patients and Methods

Study design: A Case control study conducted on 90 elderly patients aging 60 years old or more and was classified to three groups Group A: 30 diabetic patients with comorbid diseases (mainly coronary artery disease) Group B: 30 diabetic patients without comorbid diseases Group C: 30 apparently healthy non-diabetic patients as the control group.

Methodology

All patients will be subjected to

1. Comprehensive geriatric assessment
2. Investigations:

a) Laboratory

- Fasting and 2hr post prandial blood glucose level
- Lipid profile (TG, Total cholesterol, HDL, LDL).
- Total Advanced glycation end products level using Human Advanced Glycation End Products (AGEs) ELISA kit.

b) Radiological Assessment

- Ultrasound evaluation of abdominal aortic diameter (AAD) at the level of iliac bifurcation.
- Ankle Brachial Index (ABI) with hand held doppler.

Ethical Considerations

Informed consent was taken from every elderly participating in this study. The study methodology was reviewed and approved by the Ethical committee of Faculty of Medicine, Ain Shams University, Cairo, Egypt.

Statistical Methods

Analysis of data was done using SPSS 12 (statistical program for social science version 12). Description of quantitative variables was done as mean, SD and range. Description of qualitative variables was done as numbers and percentages. Chi-square test was used to compare qualitative variables between groups. The level of significance was taken at P value; P value ≥ 0.05 is insignificant, $P<0.05$ is significant, and $P<0.01$is highly significant.

Results

The demographic characteristics of the studied population are shown in Table 1. AGEs were higher in the control group than other groups. The mean AGEs level was significantly higher in the control group than in the diabetic with comorbid diseases group (group A), 211 ng/L vs 171.83 ng\ L respectively ($p < 0.022$) , and also higher in the control group than group B (diabetics without comorbidities) though not statistically significant (211 ng/L vs 204.5 ng/L respectively).

When comparing the studied population as regard the coronary risk, the 10-year coronary risk was significantly lower in the control group than other groups [calculated using the ASCVD (atherosclerotic cardiovascular disease) algorithm published in 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk].

When comparing AGEs as regard comorbid conditions among the diabetics with comorbid diseases group (group A), in our study the mean level of AGEs was higher in non-ischemic than ischemic patients (180.7 ng\L vs 165

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ng\L), higher in patients without heart failure than those with heart failure (173.571 ng\L vs 170.3 ng\ L), and higher in patients without previous stroke than those with previous stroke. (173.9 ng\L vs 168 ng\L).

No significant correlation was found between AGEs and abdominal aortic diameter in our study. As regard AGES and PAD, in our study there was statistically significant inverse correlation between AGEs and ABI among group B (diabetics without comorbidities).

Table 1 : Demographic characteristics, AAD, ABI and coronary risk among study population :

		Groups						**P-value**
		Group C		**Group B**		**Group A**		
Age	**Range**	60 - 80		60 - 75		60 - 85		0.079
	Mean ±SD	65.633 ± 6.009		64.300 ± 3.743		67.533 ± 6.372		
Sex	**Male**	9	30.00	12	40.00	10	33.33	0.709
	Female	21	70.00	18	60.00	20	66.67	
AAD *(in cm)*	Range	1.4- 2.5		1.3-2.6		1.3-3.7		0.157
	Mean ±SD	1.79 ±0.292		1.853 ±0.359		1.983 ±0.484		
ABI	Range	0.77-1.3		0.74-1.2		0.7-1.2		0.101
	Mean ±SD	0.978±0.096		0.956±0.090		0.925±0.097		
10-year Coronary risk (%)	Range	2.2-19.2		4.4-48.3		6.4-38.9		0.001
	Mean ±SD	7.562±5.241		18.2±11.704		19.300±9.542		

Table 2 :Description of Advanced Glycation End-products (AGEs) among study groups

AGES	**Groups**			**ANOVA**		**TUKEY'S Test**		
	Group C	**Group B**	**Group A**	**F**	**P-value**	**C&B**	**C&A**	**B&A**
Range	115 - 400	50 - 300	50 - 300	4.193	0.018*	0.895	0.022*	0.068
Mean ±SD	211.000 ± 59.181	204.500 ± 54.935	171.833 ± 54.194					

Table 3 :Correlation between ABI and AGEs among study groups

Correlations		
ABI	**AGES**	
	R	**P-value**
Group C	0.085	0.655
Group B	-0.534	0.002*
Group A	0.225	0.231

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Table 4 :Correlation between AAD and AGEs among study groups:

Correlations		
AAD	**AGES**	
	R	**P-value**
Group C	-0.270	0.150
Group B	0.322	0.082
Group A	-0.013	0.947

Table 5 : Comparison of subjects' comorbidities as regard AGEs among group 3 :

Group A		**AGES**				**T-Test**	
		N	**Mean**	**±**	**SD**	**T**	**P-value**
ISHD	**Yes**	17	165.000	±	61.441	-0.784	0.439
	No	13	180.769	±	43.725		
HTN	**Yes**	24	173.125	±	59.560	0.257	0.799
	No	6	166.667	±	26.013		
HF	**Yes**	16	170.313	±	57.720	-0.162	0.873
	No	14	173.571	±	51.977		
Stroke	**Yes**	11	168.182	±	46.652	-0.276	0.784
	No	19	173.947	±	59.245		

Discussion

Information on the significance of Advanced Glycation End products (AGEs) in elderly subjects is limited. So this study was conducted to determine the association between AGEs and coronary risk factors and its association with abdominal aortic diameter and peripheral arterial disease in elderly diabetics .

Comparing AGEs among the study groups revealed that AGEs were higher in the control group than other groups, and by comparing AGEs among diabetic patients with comorbidities(group A) as regard the comorbid diseases, the mean level of AGEs was higher in non-ischemic than ischemic patients (180.7 ng\L vs 165 ng\L), higher in patients without heart failure than those with heart failure (173.571 ng\L vs 170.3 ng\ L), and higher in patients without previous stroke than those with previous stroke. (173.9 ng\L vs 168 ng\L).These findings are in frank contrast to our hypothesis, since it has been widely thought that abnormal glucose metabolism leads to the increased endogenous generation of systemic AGEs which in turn plays a central role in accelerating diabetic complications. However our findings are consistent with a study carried by ***Semba et al., 2010***, who found no evidence that serum carboxymethyl lysine (CML), a dominant AGE, is associated with impaired glucose metabolism. Also, they found adults with elevated serum CML were less likely to show impaired or diabetic 2-hour plasma glucose concentrations on oral glucose tolerance testing.[8]Also***Busch et al., 2006***, found in their study that preexisting vascular disease, older age, and albuminuria are linked to increased cardiovascular risk, whereas CML level is not.[9]

No significant direct correlation was found between AGEs and abdominal aortic diameter in our study. Our results agreed with ***Norman et al., 2009*** study, that has shown circulating concentrations of carboxymethyl lysine (CML) a marker of advanced glycation, are reduced in older diabetic men with AAAs.[10]

As regard AGES and PAD, in our study there was statistically significant inverse correlation between AGEs and ABI among group B (diabetics without comorbid diseases).***Takahashi et al., 2011***, examined pentosidine (advanced glycation end product) levels and a variety of cardiovascular risk factors in healthy male individuals. The authors noted that serum pentosidine levels were an independent determinant of ABI levels.[11]In contrast, ***Prasad et al., 2016*** found no statistically significant association between the ABI and serum levels of total AGE or CML.[12] Using autofluorescence, ***de Vos et al., 2013***, also noted a poor correlation between ABI level and AGE deposition.[13]

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Several factors might explain the apparent contrasting findings between our study and the experimental work that has supported a causal role of AGEs in the development of diabetes-related vascular complications. First, many factors such as dietary intake of AGEs**,** aging , renal function[11]and use of lipid-lowering medications [12]may influence the concentrations of AGEs in tissues and plasma. In addition, plasma levels of the measured AGEs in this study may not adequately represent tissue AGE accumulation, because intracellular glycation is thought to be the major local source of AGEs[13]and not all AGEs may end up in the circulation.

Conclusion

Although experimental studies highlighted the importance of the AGEs in the pathogenesis of CVD, our study suggests that the use of plasma levels of these AGEs as biomarkers for increased CVD risk in elderly population may be limited. And therefore, alternative measurements of AGEs burden, such as free methylglyoxal, AGEs in circulating cells, urine, or tissue might be of greater relevance compared with serum levels, which remains open to further study

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