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Full Length Research Paper

Oxidative stress in myocardial infarction: Advanced glycation end-products causes oxidative stress in older myocardial infarction patients

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Older patients with type 2 diabetes mellitus have a two- to four-fold increased risk of myocardial infarction. This study aims to determine the association between oxidative stress and advanced glycation end product (AGE). Human serum samples from normal older subjects (*n* = 31), older diabetic patients without myocardial infarction (*n* = 33), older diabetic patients with myocardial infarction (*n* = 32), older non-diabetic with myocardial infarction (*n* = 30) and normal young subjects (*n* = 31) were investigated. Positive significant correlation was observed between serum AGE and malondialdehyde in older diabetic and non-diabetic patients with myocardial infarction. Negative significant correlation was observed between AGE and vitamin-E in older diabetic and non-diabetic patients with myocardial infarction. However, malondialdehyde and serum AGE were found to be significantly (P < 0.001) higher in older diabetic and non-diabetic patients with and without myocardial infarction as compared with older control subjects. In contrast to all four older groups, the serum AGE was significantly (P < 0.001) lower in young control subjects. This study revealed that AGE was positively associated with markers of oxidative stress in the older groups.

Key words: Advanced glycation end products, myocardial infarction, diabetes.

INTRODUCTION

Type 2 (non-insulin dependent) diabetes mellitus, the most prevalent form of the disease, is associated with chronic macrovascular and microvascular complications. In the developed world, the risk of myocardial infarction is increased two to four-fold among diabetic patients compared with non-diabetic persons (Aronson, 2008; Saleheen and Frossard, 2004). Recently, it has been documented that, among various factors, advanced glycation end products (AGEs), a heterogeneous group of irreversibly modified products formed in excess during aging and diabetes mellitus, play a crucial role in this process (Vlassara and Palace, 2003). Hyperglycemia can stimulate non-enzymatic glycation and oxidation of proteins and lipids, leading to enhanced formation of AGEs, which may be involved in the pathogenesis of diabetic vascular diseases (Soldatos and Cooper, 2006).

The presence of AGEs has also been reported in atherosclerotic plaques, and the cross-linking abilities of AGEs may contribute to the increased stiffening of collagen and possibly to vascular hypertrophy (Price and Knight, 2007). Accumulation of AGEs with structural alterations results in altered tissue properties that contribute to the reduced susceptibility of catabolism (Baynes and Thorpe, 2000). Another possible mechanism by which AGEs may contribute to development of atherosclerosis is by activating the transcription nuclear factor κB (NF-κB) through RAGE

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binding, resulting in induction of cellular adhesion molecule expression and cytokine activation or through glycoxidation of lipoproteins and increased foam cell formation (Bierhaus et al., 1997).

Reactive oxygen species (ROS) generated in oxidative stress from a variety of sources can in turn accelerate AGE formation. Oxidative stress originates due to an imbalance between the generation of ROS and the antioxidant defense system. Production of ROS depletes antioxidants and antioxidant enzymes, leading to additional ROS accumulation. AGE formation is dependent on oxidative processes and can create ROS through the Millard reaction (Yamagishi and Imaizumi, 2005). One of the most frequently used biomarkers providing an indication of the overall lipid peroxidation level is the plasma concentration of malondialdehyde (P-MDA), one of several byproducts of lipid peroxidation processes. An increased production of ROS and an enhanced concentration of thiobarbituric acid-reactive substances (TBARs) resulting in oxidative stress, have been observed in diabetes (Surekha et al., 2007). The level of serum AGE could be considered as a marker for the developments of myocardial infarction in older diabetic, as well as in non-diabetic patients.

MATERIALS AND METHODS

Subjects and sample collection

The study included one hundred fifty seven subjects. Out of these, 31 were normal older subjects, 33 were older diabetic patients without myocardial infarction, 32 were older diabetic patients with myocardial infarction, 30 were older non-diabetic with myocardial infarction and 31 were normal young subjects. The blood samples were collected from the subjects during the period of March, 2004 to December, 2007. The ethical committee of Ziauddin University approved the protocol, and consent of the patients was obtained after the nature of the study was fully explained. The older subjects were selected who were over sixty years of age, and young, apparently healthy (age ranging from 20 to 25 years) were selected as control subjects. Sex, weight, duration of diabetes, duration of complication in diabetic and non-diabetic patients, type of diabetes and type of treatments received were also recorded. Physical examination, including measurement of blood pressure was recorded.

Individuals were classified as having diabetes mellitus if any of the following criteria were met (Gabir et al., 2000); fasting serum glucose levels of 7.0 mmol/L or more, random glucose levels of more than 11.1 mmol/L, current use of medications prescribed to treat diabetes (for example, insulin or drugs). Older patients, those with more than one complication, and type 1 diabetics, were excluded from the study. Diagnosed cases of myocardial infarction were included in the study on the basis of chest pain, Electrocardiography (ECG) changes that is, ST elevation and Q wave inversion and biochemical markers that is, raised levels of troponin T, creatine kinase MB (CKMB), aspartate aminotransferase (AST) and Lactate dehydrogenase (LDH). The patients were selected on clinical grounds from National Institute of Cardiovascular Disease, Karachi and Jinnah Postgraduate Medical Centre, Karachi, Pakistan.

Blood was collected in fasting state after a 10 h overnight fast. Samples were withdrawn by venous puncture and distributed equally into three tubes containing ethylenediaminetetraacetic acid (EDTA) (for $HbA1_C$), heparin (for glucose estimation) and tube with no anti-coagulant (for serum collection). The samples were then immediately stored on ice until processed. Clotted blood was centrifuged at 1,500 rpm for 30 min and the serum was separated and frozen at -70°C until analysis. Blood glucose was determined by glucose oxidase method, glycosylated hemoglobin ($HbA1_C$) was determined calorimetrically using HbA_{1C} kit (Bio Systems Reagents and Instruments, Spain). The serum fructosamine was determined calorimetrically using fructosamine kit (Randox, UK). Vitamin-E was measured on the basis of the reduction of ferric ions to ferrous ions by α-tocopherol and subsequent formation of a pink colored complex with bathophenanthroline which was measured colorimetrically at 536 nm (Baker et al., 1980). Malondialdehyde of the serum sample was reacted with thiobarbituric acid to form a pink coloured pigment, the absorbance of which was measured at 535 nm (Valenzuela, 1991).

Determination of AGEs

Pretreatment of the serum samples for AGEs measurement

To 100 µl of serum diluted with 100 mM phosphate-buffered saline (PBS), pH 7.2 (PBS), 100 µl of 0.6% Sodium dodecyl sulfate (SDS)/10 mM Tris-HCl saline, pH 7.4 and 5 µl of 2 M $NaBH_4$/50 mM NaOH was added. The mixture was immediately heated at 100°C for 10 min. After cooling in ice water, a further 800 µl of PBS was added and the samples were then used for AGE assay.

Generation of bovine serum albumin (AGE-BSA) standard

AGE-BSA was prepared by incubating 5 g BSA with glucose (0.56 M) in PBS under sterile conditions for sixteen weeks at 37°C. Samples were dialysed against PBS and stored at -70°C, protected from light until used. The amount of AGE was determined by non-competitive Enzyme-linked immunosorbent assay (ELISA) using rabbit polyclonal antibodies to AGE (Abcam, UK) (Ono et al., 1998). A 96-wells microplate was coated with 200 µl of sample and its corresponding control in 50 mM sodium bicarbonate buffer (pH 9.6) and kept at 4°C overnight. After overnight incubation, the wells were washed four times using PBS containing 0.05% Tween-20 (PBST). Each well was blocked for two hours with blocking buffer, washed four times with PBST and incubated with 200 µl of $1:10^4$ diluted anti-AGE antibody for 2 h. After washing wells four times, 200 µl of 1:2000 diluted horseradish peroxidase (HRP)-anti-rabbit immunoglobulins (Abcam, UK) were added to each well and incubated for 2 h. Wells were washed five times and reacted with 200 µl of 3,3',5,5'-tetramethylbenzidine (TMB) solution which was added to each well and incubated for 30 min, and absorbance at 650 nm was measured. Results were expressed as arbitrary AGE units (1 mU of AGE corresponds to 4 µg of AGE-bovine serum albumin (BSA) standard).

Statistical analysis

Data was analyzed using Statistical Package for Social Sciences (SPSS, v 10.0) (SPSS Inc., Chicago, Illinois). The results were presented as mean ± standard error of mean (SEM) and standard deviation (SD). The statistical significance of the difference between two mean of various parameters between different groups was evaluated by one-way analysis of variance (ANOVA). The Bonferroni's post hoc test was used to determine which group means differed. With this test, SPSS automatically adjusted the significant level for the multiple comparisons to avoid spurious significant differences being identified (any values below the level of 0.05 was considered as significant) Table 1.

Table 1. Physical features and blood analysis of young healthy subjects, older control subjects, older diabetic patients without myocardial infarction and older diabetic and non-diabetic patients with myocardial infarction**.**

Parameter	Young Healthy Subjects (31)	Older control subjects (31)	Older diabetic patients without myocardial infarction (33)	Older diabetic patients with myocardial infarction (32)	Older non-diabetic patients with myocardial infarction (30)
Age (years)	21.93±0.28	64.19[a]±0.70	64.18± 0.57	66.00±0.78	65.73±0.85
Sex (F/M)	16/15	16/15	16/17	14/18	15/15
Weight (kg)	59.06±1.11	63.61±1.22	65.66±1.53	66.03±1.07	63.33±1.26
Height (m)	1.59±0.01	1.59±0.01	1.59±0.01	1.58±0.01	1.60±0.01
BMI (kg/m^2)	23.39±0.48	25.22±0.53	26.00±0.64	26.20[c]±0.51	24.78±0.57
Systolic BP (mmHg)	119.51±1.12	121.54±1.05	119.70±1.19	144.53[b]±4.29	139.16[b]±4.53
Diastolic BP (mmHg)	79.19±1.01	83.06±1.10	81.66±1.05	91.56[b]±1.67	87.33[b]±1.80
Fasting Blood Glucose (mmol/l)	4.88±0.09	5.09±0.10	7.46[b]±0.24	8.97[bc]±0.29	5.07±0.12
Glycosylated Hemoglobin (HBA1c %)	4.81±0.07	4.97±0.08	9.02[b]±0.28	9.26[bc]±0.26	5.09±0.10
Serum Fructosamine (mmol/l)	2.10±0.06	2.33±0.06	3.79[b]±0.11	3.74[bc]±0.11	2.08±0.10
Serum-AGEs (mU/ml)	1.71±0.25	04.97a±0.34	8.10[b]±0.49	13.78[bc]±0.30	9.55[b]±0.27
Malondialdehyde (nM/ml)	-	3.56±0.26	7.06[b]±0.30	14.33[bc]±0.53	10.03[b]±0.36
Vitamin-E (mg/dl)	-	1.66±0.06	0.89[b]±0.05	0.78[bc]±0.05	1.23[b]±0.04

The values are expressed as mean, ± standard error of mean. Units and numbers of cases are shown in parentheses. [a]Significant as compared with young healthy subjects, [b]significant as compared with older control subjects, [c]significant as compared with non-diabetic older patients with myocardial infarction.

RESULTS

Concentrations of malondialdehyde and serum AGEs were significantly higher ($P < 0.001$) in older diabetic patients with and without myocardial infarction and older non-diabetic patients with myocardial infarction as compared with the older control subjects. When compared with older diabetic patients without myocardial infarction, AGE and malondialdehyde were highest in older diabetic patients with myocardial infarction. Serum vitamin-E was found to be significantly ($P < 0.001$) lower in older diabetic patients with and without myocardial infarction as compared with the older control subjects. The normal older subjects showed significantly elevated in AGE ($P < 0.001$) as compared with normal young subjects. Fasting blood glucose, HbA_{1C} and serum fructosamine were significantly increased in older diabetic patients with or without myocardial infarction as compared with older non-diabetic patients with myocardial infarction and older control subjects. The increase in the fasting blood glucose level in all older diabetic patients with and without myocardial infarction correlates significantly with glycosylated hemoglobin and serum fructosamine concentrations. Also, the fasting blood glucose, glycosylated hemoglobin and serum fructosamine were not found to be different in older diabetic patients with and without myocardial infarction. When compared with age matched normal subjects, the older non-diabetic patients with myocardial infarction showed no significant difference in levels of fasting blood glucose, glycosylated hemoglobin and serum fructosamine.

A significantly positive correlation was observed between serum AGEs and malondialdehyde ($r = 0.92$) in diabetic patients with myocardial infarction and in non-diabetic patients with myocardial infarction ($r = 0.98$) (Figures 1 to 4). Significant negative correlations were observed between serum AGEs and vitamin-E ($r = -0.87$) in diabetic patients with myocardial infarction, in non-diabetic patients with myocardial infarction ($r = -0.94$) and between malondialdehyde and

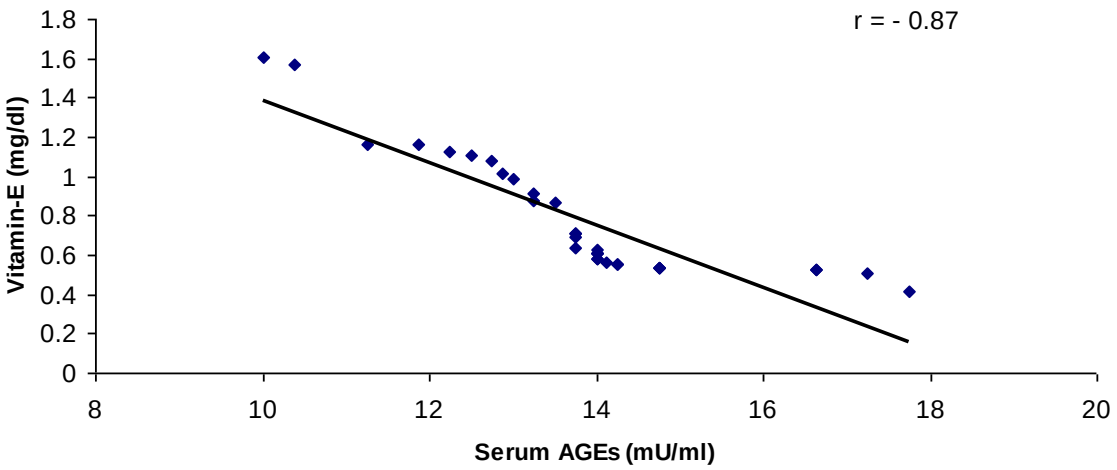

Figure 1. Correlation of serum AGEs versus vitamin-E in diabetic patients with myocardial infarction.

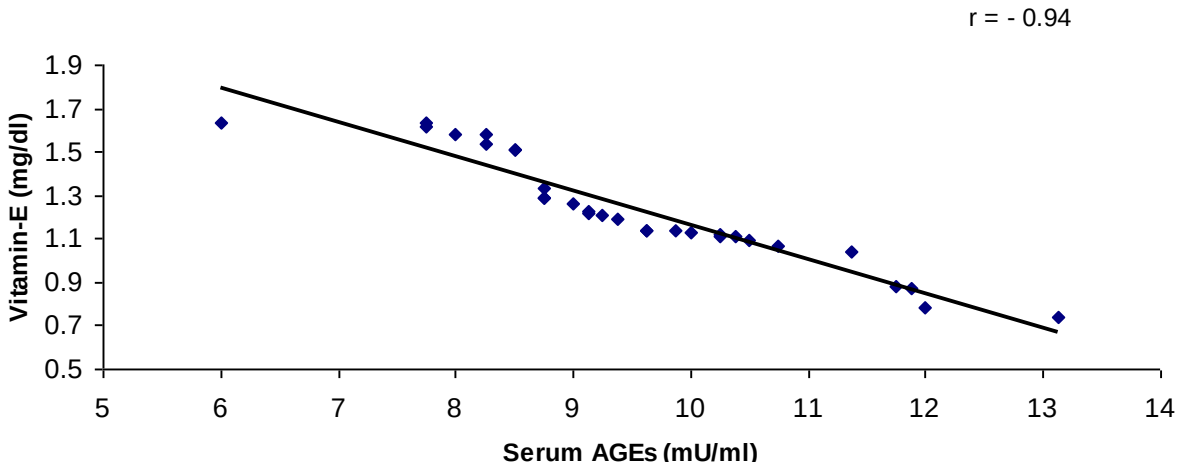

Figure 2. Correlation of serum AGEs versus vitamin-E in non-diabetic patients with myocardial infarction.

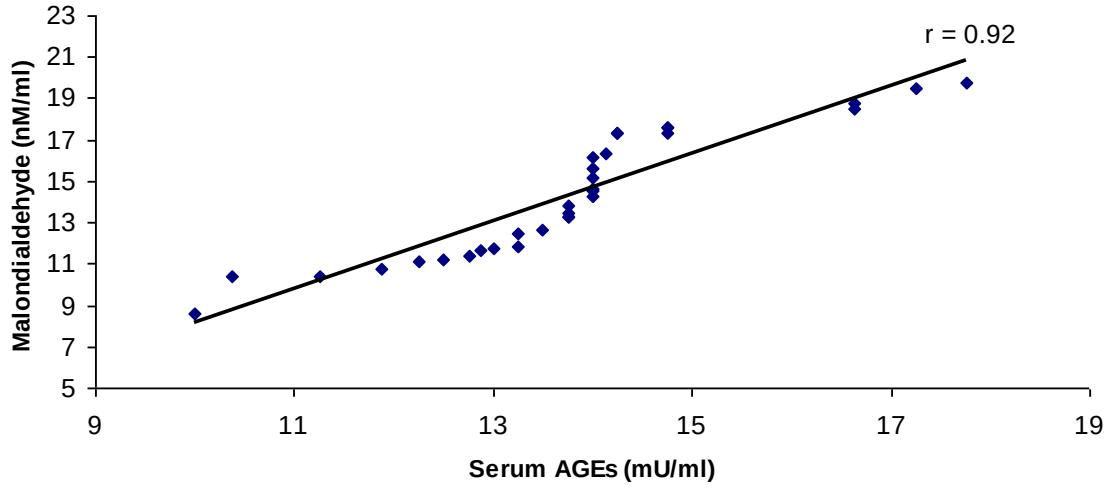

Figure 3. Correlation of serum AGEs versus malondialdehyde in diabetic patients with myocardial infarction.

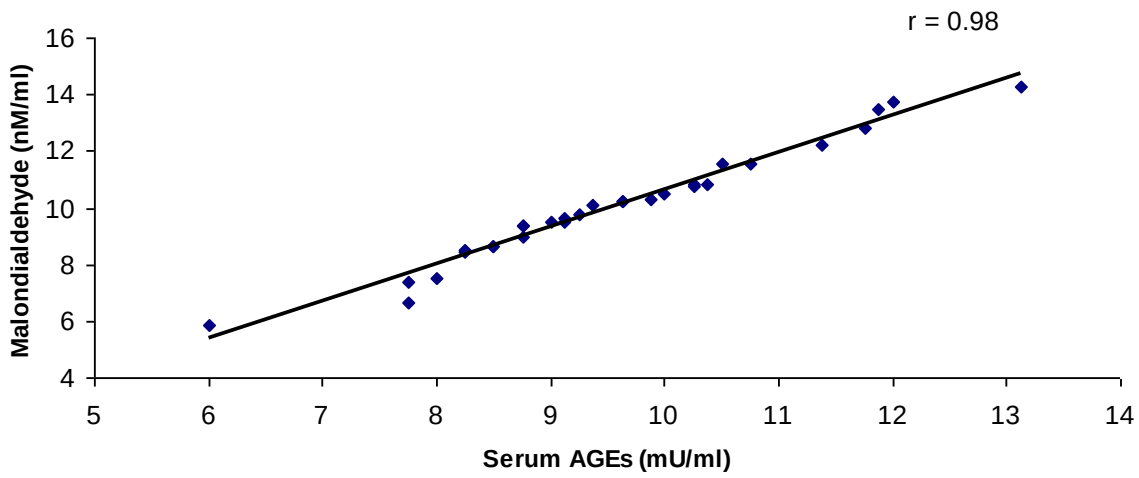

Figure 4. Correlation of serum AGEs versus malondialdehyde in non-diabetic patients with myocardial infarction.

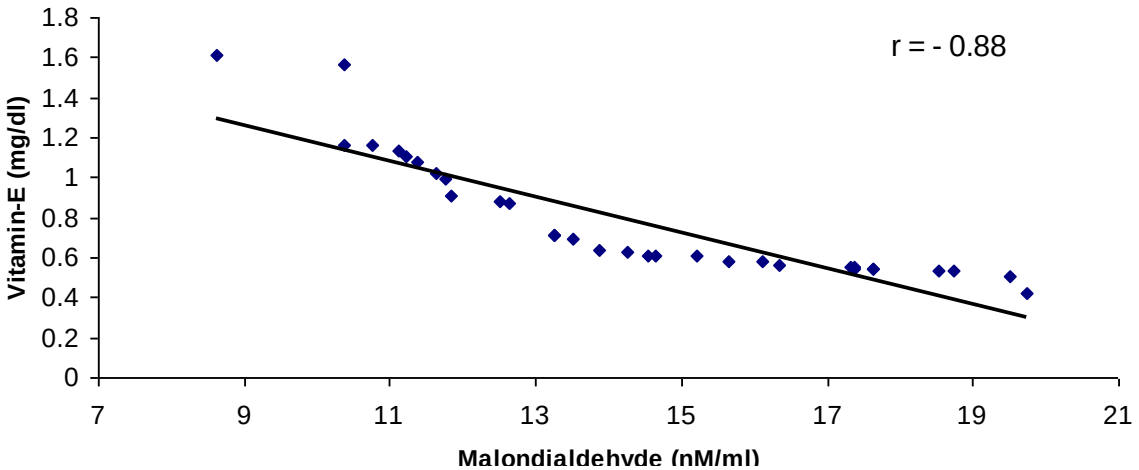

Figure 5. Correlation of malondialdehyde versus vitamin-E in diabetic patients with myocardial infarction.

vitamin-E in diabetic patients with myocardial infarction (r = -0.88) (Figure 5).

Significant positive correlations were observed between fasting blood glucose and serum fructosamine (r = 0.96), systolic blood pressure (r = 0.91), serum AGEs (r = 0.94) and between systolic blood pressure and serum AGEs (r = 0.89) in diabetic patients with myocardial infarction.

DISCUSSION

In the present study, the increased levels of malondialdehyde and decreased vitamin-E clearly show that diabetic patients, irrespective of the gender, were exposed to an increased oxidative stress via lipid peroxidation. This could be due to failure of antioxidant defense system; the ROS accumulates and initiates lipid peroxidation (Kunitomo, 2007). In the present study, antioxidant defense mechanism by vitamin-E and oxidative stress causing agent by malondialdehyde in older diabetic and non-diabetic patients with and without myocardial infarction, were investigated. Malondialdehyde levels were significantly higher ($P < 0.001$) in older diabetic patients with or without myocardial infarction and older non-diabetic patients with myocardial infarction as compared with older control subjects. In addition, serum vitamin-E was found to be significantly decreased ($P < 0.001$) in older diabetic patients with and without myocardial infarction as compared with older control subjects. Present results are consistent with earlier reports indicating an elevated level of serum lipid peroxide and diminished antioxidant status in diabetic patients (Senthil et al., 2004).

Decreased antioxidant activity and high concentration of lipid peroxidation product may lead to oxidation proteins resulting in myocardial infarction. Our results confirm previous data of enhanced ROS levels in diabetes mellitus (Schleicher and Friess, 2007). Yan et

al. (1994) showed that interaction of AGEs with endothelial cells leads to oxidative stress by a receptor-mediated process. AGE might induce oxidative stress through chemical and cellular mechanisms. In addition to the monosaccharides, the AGEs have also been reported to be produced from dicarbonyl compounds derived from the Millard reaction, autoxidation of sugars and other metabollic pathways for example, glycolysis, and this can account for the increase in the serum AGE in non-diabetic patients with myocardial infarction (Peppa et al., 2004).

Recent studies have brought new insights into broad derangements in non-enzymatic glycation involving not only carbohydrates but also lipids present in diabetes, uremia and atherosclerosis (Chuyen, 2006). Increased level of AGE content in diabetic state was reported earlier (Ahmed, 2005). The results of this study are also being in accordance with these reports. Therefore, it can be speculated that the AGE structures resulting from persisting hyperglycemia are more profusely formed in diabetes and the fact that tissue levels of AGE correlate with prevailing serum concentrations of glucose, fructosamine and glycated hemoglobin, points to a role for hyperglycemia, yet there is good evidence that other carbohydrates such as ascorbate, pentoses may act as potent glycating agents (Dyer, 1991).

People with diabetes are prone to long-term complications such as myocardial infarction, and development of such complications is a major cause of morbidity and mortality and an ever-increasing burden to healthcare authorities in both developed and developing nations (Veiraiah, 2005). Epidemiological studies have confirmed that hyperglycemia is the most important factor in the onset and progress of vascular complications in diabetes (Shera, 1998). The formation of AGEs correlates with glycemic control. The AGE hypothesis proposes that accelerated chemical modification of proteins by glucose during hyperglycemia contributes to the pathogenesis of diabetic complications, including atherosclerosis (Yamagishi et al., 2007).

Glycation has both physiological and pathophysiological significance. Under physiological conditions, glycation can be detected in the ageing process, and the reactions are more rapid and more intensive with frequently increased glucose concentrations (Ulrich and Cerami, 2001). The AGE concept proposes that chemical modification and crosslinking of tissue proteins, lipids and DNA affect their structure and function. This in turn contributes to a gradual decline in tissue function and to the pathogenesis of myocardial infarction in diabetic and in non-diabetic patients (Xanthis et al., 2007; Kanauchi et al., 2001). AGEs have previously been shown to accumulate in many tissues with age, independently of diabetes (Lingelbach et al., 2000). Since the body does not contain any single enzyme capable of AGE structure degradation, AGEs accumulate during the biological life of proteins on which they had been formed (Yan et al., 2006). In addition to the diabetic patients, the serum AGEs was also found to be higher in the older non-diabetic patients with myocardial infarction as compared with older diabetic patients without myocardial infarction, however, this increase was not significant. It states that the role of AGEs in diabetic and non-diabetic patients is potentially important because it induces both the structural and functional implications.

Environmental conditions can results in the formations of various AGEs by a variety of chemical reactions, and the reasons for the formation of such structures in non-diabetic conditions are difficult to explain. Studies have suggested the role of oxidative stress in the formation of AGEs structures, therefore, it might be postulated that reactive oxygen intermediates may accelerate the rate of AGE formation through reactive oxoaldehydes and vice versa; AGEs might induce oxidative stress through chemical and cellular mechanisms (Basta et al., 2005; Miyata et al; 2003). The observations of older groups increased as compared with that of young normal subjects.

Conclusion

Thus, the results of this study support the hypothesis that AGEs may have an important role in myocardial infarction, which in diabetic patients occur much earlier than in those without diabetes. This study also revealed that increased AGEs associated with oxidative stress in the older groups. Taken together the above facts and results, it can be postulated that utilization of antioxidant rich food, along with low AGEs content diet, may be beneficial in delaying myocardial infarction progression, particularly in diabetic subjects.

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