Serum Levels of Antibodies to Advanced Glycation End Products in Patients with Type 2 Diabetes Mellitus and Hypertension

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Abstract

Background and Aims: Proteins containing advanced glycation end products are highly immunogenic and anti-advanced glycation end products antibodies (anti-AGEs antibodies) are found in the sera of diabetics.

Materials and methods: Enzyme-linked immunosorbent assay (ELISA) was used for measuring levels of anti-advanced glycation end products antibodies in sera of 93 patients with type 2 diabetes mellitus and arterial hypertension (mean age 61.4±11.3 years, diabetes duration 9.88±3.12 years; hypertension duration 9.28±4.98). These values were compared to serum anti-AGEs antibodies in 42 age and sex matched controls. Diabetics were divided in two groups according to presence or absence of microangiopathy, group 1 (n=67) and group 2 (n=26), respectively.

Results: Serum levels of anti-AGEs antibodies in patients with type 2 diabetes mellitus and arterial hypertension were statistically significantly higher than those in the control group (1.39±0.39 vs. 1.05±0.32), (p<0.05). Group 1 showed significantly higher levels of anti-AGEs antibodies than those of healthy controls (1.53±0.14 vs. 1.05±0.32), (p<0.01). Anti-AGEs antibodies levels were higher in patients with microvascular complications than these in patients without complications. Anti-AGEs antibodies correlate with diastolic blood pressure (r=0.26, p=0.05) and body mass index (r=0.37, p=0.03). We found significantly higher percentage of positive patients for anti-AGEs antibodies (mean+2SD) in group 1 than in group 2.

Conclusion: Determining the levels of serum anti-AGEs antibodies can help physicians make early diagnosis and prognosis of the severity of late diabetic complications in hypertensive patients.

Keywords

anti-advanced glycation end products antibodies, arterial hypertension, diabetic microvascular complications

INTRODUCTION

Non-enzymatic glycation of proteins or lipids can lead to the formation of reactive advanced glycation end products (AGEs), which are thought to be implicated in the formation of micro- and macrovascular complications in diabettes.¹-⁴ Long living proteins such as collagen, elastin, lens crystalline and DNA are particularly susceptible to AGE modification.⁵ In our previous studies, we found elevated serum levels of anti-collagen type IV and anti-elastin antibodies in patients with type 2 diabetes mellitus with microangiopathy.⁶-⁷ Reactive AGE can directly alter the physical
and structural properties of the extracellular matrix (ECM) by inducing collagen cross-linking, basement membrane thickening and covalent trapping of plasma proteins such as low density lipoprotein (LDL) and immunoglobulin G (IgG).\textsuperscript{8,9} AGEs may exert their effects via their interactions with specific receptors initially identified on macrophages, monocytes and endothelial cells.\textsuperscript{10,11} Localization of AGEs and their receptors at sites of microvascular injury indicates that subsequent interaction may be a mechanism for the development of diabetic microvascular complications. AGEs can increase protein crosslinking and this could reduce tissue elasticity and decrease protein turnover.\textsuperscript{12-14}

AGEs are special products belonging to a heterogeneous group of chemical components formed through non-enzyme glycation i.e. through connection of reduced glucose molecule (also known as glyco-oxygenation or glycosylation) with proteins, fats and nucleic acids. The term final product is chosen because AGEs are the final products of chain reactions generating some oscillant products such as Schiff bases, Amadori products, Maillard products, deoxyglucosone, and methylglyoxal glycolaldehyde. Carboxymethyl lysine (CML), carboxyethyl lysine (CEL), pentosidine, and hydroimidazolone are some of the most important examples. CML is known as AGEs-indicator.\textsuperscript{15}

AGEs and the receptors against AGEs (RAGE) can be detected in almost every body cell. This fact suggests the major role they play in the progress of atherosclerosis, especially in patients with diabetes mellitus. The AGEs concentrations in the serum of type 2 diabetes are significantly higher than those in healthy individuals and this is related to a higher cardiovascular mortality rate. Accumulation of AGEs is related with the development and progression of late injury of diabetes independently of HbA1c levels, so in this way metabolic stress rises.\textsuperscript{16,17}

Proteins containing AGE are highly immunogenic\textsuperscript{18} and anti-advanced glycation end products antibodies (anti-AGEs antibodies) are found in sera of patients with diabetes mellitus. The AGEs concentrations in the serum of type 2 diabetes are significantly higher than those in healthy individuals and this is related to a higher cardiovascular mortality rate. Accumulation of AGEs is related with the development and progression of late injury of diabetes independently of HbA1c levels, so in this way metabolic stress rises.\textsuperscript{16,17}

Antigen preparation
AGE-elastin was obtained via incubation of human aortic \(\alpha\)-elastin (1.33 mg/ml\textsuperscript{-1}) with 100 mmol/l\textsuperscript{-1} glucose, in 0.2 M phosphate buffer, pH 7.8, containing 0.04% sodium azide, at 37\textdegree C for 30 days as described in Baydanoff et al.\textsuperscript{20}

Production of immune serum
Polyclonal immune serum against AGE of Hemocyanin from Keyhole Limpets (AGE-KLH) was produced in guinea pig as described by Baydanoff et al.\textsuperscript{20}

Measurement of anti-AGE antibodies in human sera
A blocking enzyme-linked immunosorbent assay (ELISA) was used for detection of antibodies to advanced glycated end products.\textsuperscript{20} The wells of polystyrene plates were coated with AGE-elastin (5 µg/ml). After washing, the wells were incubated with 100 µl of human sera (diluted 1:20) for 1 h at 37\textdegree C. The plates were washed and the wells were incubated with 100 µl guinea pig anti-AGE-KLH immune serum (diluted 1:1000) for 1 h at 37\textdegree C. The plates were then washed and goat anti-guinea pig IgG peroxidase immunocjugate (SIGMA, USA) diluted 1:10 000 was used for 1 h incubation at 37\textdegree C. The reaction was stopped by the addition of 50 µl 4 M H\textsubscript{2}SO\textsubscript{4}. The reactivity of the immune serum without added human serum was used as a control.
Anti-AGEs Antibodies in Patients with Diabetes Mellitus and Hypertension

Table 1. Clinical data of patients with type 2 diabetes and arterial hypertension

| Clinical Data                  | Group 1            | Group 2            | Controls        |
|-------------------------------|--------------------|--------------------|-----------------|
| Age                           | 62.5±12.58         | 60.4±8.4           | 58.9±7.56       |
| Sex (male/female)             | 26/41              | 11/15              | 20/22           |
| Average duration of diabetes  | 9.30±5.36          | 9.16±7.59          | N/A             |
| Average duration of hypertension | 9.50±7.63     | 8.68±7.26          | N/A             |
| HbA1c                         | *7.63±2.03         | 7.27±1.63          | N/A             |
| Systolic blood pressure (mmHg)| 142.83±18.05       | 140.58±20.51       | 114.29±15.74    |
| Diastolic blood pressure (mmHg)| 82.23±11.52      | 81.35±11.96        | 72.5±10.4       |
| Body mass index               | 29.62±4.99         | 28.42±3.96         | 22.61±2.27      |
| Total cholesterol (mmol/l)    | *5.26±1.40         | 5.18±0.93          | 3.99±0.65       |
| HDL (mmol/l)                  | *0.88±0.30         | 0.93±0.30          | 0.96±0.20       |
| LDL (mmol/l)                  | 3.18±1.19          | 3.16±1.09          | 2.43±0.64       |
| Triglycerides (mmol/l)        | 2.91±1.68          | 2.53±1.49          | 1.31±0.61       |
| Insulin dose (U/kg/24h)       | 2.57±0.52          | 2.03±0.93          | N/A             |
| Microalbuminuria (µg/min)     | *78.94±52.87       | 8.53±4.69          | N/A             |
| Number of patients with microalbuminuria | (n=43) | -                 |
| Number of patients with retinopathy | (n=20)    | -                 |
| Number of patients with neuropathy | (n=4)     | -                 |
| Smokers                       | 37/67              | 15/26              | 16/42           |
| Total number of patients      | 67                 | 26                 | 42              |

Group 1: patients with vascular complications (n=67); Group 2: patients without vascular complications (n=26); Controls (n=42); HbA1c: glycated haemoglobin; HDL: high density lipoprotein; LDL: low density lipoprotein; Values are mean ± SD

Values equal to or less than the mean±2SD of healthy controls were considered positive.

Table 2. Distribution of patients in the groups by sex and presence or absence of smoking as a factor

| Groups     | Sex       | Smoking       |
|------------|-----------|---------------|
|            | Male      | Female        | Smokers | Non-smokers |
| Group 1    | 39%       | 61%           | 55%     | 45%         |
| Group 2    | 42%       | 58%           | 58%     | 42%         |
| Controls   | 45%       | 55%           | 47%     | 53%         |

Characterisation of immune antibodies

Antibodies to elastin epitopes were eliminated by two absorption steps on elastin. The anti-AGE antibodies reacted with AGE epitopes regardless of the protein. For example our antibodies recognize AGE-elastin, AGE-BSA, and AGE-KLH in ELISA. 20 AGE-peptides are also recognized. Reaction with AGE-elastin could be abolished by pre-incubation with AGE-elastin, AGE-BSA, or AGE-KLH.

Other methods

Ophthalmoscopy through dilated pupils was carried out in all diabetic patients to assess the presence of retinopathy, with all patients studied by the same ophthalmologist. Glycated haemoglobin, serum total cholesterol and triglyceride concentrations, arterial blood pressure and AER were examined as described elsewhere.

Statistical analysis

All values are expressed as mean±SD. Statistical analyses were done using the computer programs EXCEL and STATGRAPHICS plus for WINDOWS. The Student t-test and ANOVA were used to assess differences between study groups. The correlation and regression analyses were also used. The level of significance was determined as p less than 0.05.
RESULTS

A competitive ELISA was used for detection of anti-AGEs antibodies. Patients’ sera with extinction values more than mean±SD of the healthy controls at the end of the study were considered as positive.

Levels of anti-AGEs antibodies in patients with type 2 diabetes mellitus and AH were significantly increased than those in control group (1.39±0.39 vs. 1.05±0.32; p<0.05). Group 1 showed significantly higher levels of anti-AGEs antibodies than healthy controls (1.53±0.14 vs. 1.05±0.32; p<0.01). (Table 3) (Fig. 1). Anti-AGEs antibodies levels were higher in patients with microvascular complications (1.53±0.14) compared to patients without such complications (1.37±0.20) (Group 2). Antibodies against AGEs correlate with diastolic blood pressure (r=0.26); (p=0.05) and BMI (r=0.37); (p=0.03).

**Table 3.** Levels of anti-AGEs antibodies in patients with T2DM and AH

| Groups            | Anti-AGEs antibodies | Compared to others |
|-------------------|----------------------|--------------------|
|                   | Mean±SD              | Group 1 | Group 2 | All Diabetics |
| All Diabetics     | 1.39±0.39            | NS      | NS      | -            |
| Group 1           | 1.53±0.14            | NS      | NS      | -            |
| Group 2           | 1.37±0.20            | NS      | NS      | -            |
| Controls          | 1.05±0.32            | p<0.01  | p<0.05  | p<0.05       |

Anti-AGEs antibodies: antibodies against advanced glycation end products; T2DM: type 2 diabetes mellitus; AH: arterial hypertension; NS: non significant

**Figure 1.** Levels of anti-AGEs antibodies in patients with T2DM and AH. Anti-AGEs antibodies: antibodies against advanced glycation end products; T2DM: type 2 diabetes mellitus; AH: arterial hypertension

The percentage of positive patients for anti-AGEs antibodies (levels mean±2SD) was significantly higher in the group of subjects with microvascular complications than those in the group without microvascular complications. (Fig. 2):

- 6 patients from 43 (14%) with microalbuminuria were positive for antibodies against AGEs compared to 3 from 26 (10%) without microalbuminuria.
- 5 patients from 20 (25%) with retinopathy were positive compared to 4 from 26 (15%) without retinopathy.

**DISCUSSION**

Increased serum levels of antibodies recognizing AGE-modified proteins in streptozotocin-diabetic rats were reported by Shibayama et al. Isolation of IgG with similar specificity from diabetic patients’ plasma was also reported. There is an evidence for significantly higher levels of these antibodies in patients with retinopathy or renal failure caused by diabetes compared to healthy controls. We analyzed sera of diabetic patients with arterial hypertension and compared their results with those of healthy subjects. Our data confirmed that anti-AGE antibodies are increased in diabetic subjects with hypertension. Moreover we found an association between microvascular complications and serum levels of anti-AGEs antibodies. This is in accordance with the previous reports. On the other hand, six patients out of 43 (14%) with microalbuminuria were positive for anti-AGEs antibodies, and 3 from 26 (10%) without complications. Five patients from 20 (25%) with retinopathy were positive, and 4 from 26 (15%). This fact supports the hypothesis that elevation of anti-AGE antibodies can predict development of diabetic microvascular complications. The anti-AGEs positive patients with microvascular complications showed higher levels of HbA1c compared to non-positive diabetics. The accelerated nonenzymatic glycation of proteins may be the reason for formation of new AGE epitopes on the protein molecules. These new determinants may be more antigenic. We suppose that intensive glycation and formation of AGE during diabetes induce increased generation of these antibodies. Then they are involved in microvascular injury via formation of immune complexes in situ and comple-
ment binding. Our findings are supported from the data that concentrations of AGE rise with age and are approximately doubled in diabetes, correlating with the severity of diabetic microvascular disease.\textsuperscript{22} It is known that AGEs have impact on lipids’ metabolism and acceleration of atherosclerosis which could influence diabetes related vascular disease.\textsuperscript{23,24} Our data support that evidence because we found a positive correlation between anti-AGEs antibodies and total cholesterol and triglycerides in the present study.

Higher levels of reactive oxygen variety cause AGEs and atherosclerosis interaction. In result endothelial dysfunction can occur. Production of superoxide in mitochondrial electro transportation chain is identified as a central mechanism in microvascular diseases in diabetes, endothelial dysfunction and formation of AGEs. Super oxide activate DNA repair cycle through poly(ADP-ribose) polymerase. This activation leads to inhibition of glyceraldehyde-3-phospat dehydrogenase (GDPDH). This leads to blockage of metabolic system glycolysis and results in activation of other ways. Successful increase of glyceraldehyde-3-phosphate and glycerol-3-phosphate and first stage of formation of AGEs through methylglyoxal.\textsuperscript{25}

Oxidative stress activated by AGEs leads to tissue dysfunction, formation of atherosclerosis plaque and in the end stages myocardial infarction and insult can occur. That is why it is so difficult to prevent diabetes vascular injury despite good controlled blood-sugar profile UKPDS (United Kingdom Prospective Diabetes Study Group) 1998.\textsuperscript{26}

In our study we used human aortic \(\alpha\)-elastin, glycated in vitro as an antigen, expressing AGE epitopes, common to all glycated proteins. The reason is that glycation of haemoglobin forms HbA1c that has been described as an Amadori product but is not an AGE.\textsuperscript{27} It is an indicator of glycaemia from the preceding 6 to 12 weeks, whereas advanced glycation reflects a process that can occur a longer period.\textsuperscript{28} Many hypotheses for the etiology of arterial disease involve changes in the extracellular matrix and it is possible that increased susceptibility in diabetes mellitus is associated with glycation arising from reaction between glucose and the amino groups on proteins.

Collagen is an extracellular matrix protein with very important mechanical functions in many body tissues. Interestingly it has attracted an attention as a substrate for most of glycation reactions.\textsuperscript{29} This is due to the fact that collagen has very low turnover rate and it is therefore at risk of modification even by very slow chemical reactions. Elastin also requires consideration by these criteria. It has the lowest turnover rate of all matrix components and its mechanical properties are crucially important in normal arterial function. Elastin is widely implicated in pathological conditions, either through loss of its mechanical properties or because it acts as a substrate for calcification and lipid deposition. Vascular extracellular matrix and especially elastic elastin are degraded in age and atherosclerosis. Among the indexes which take part in this progress are serum concentration of elastin derived peptides and AGEs.

Biochemical analysis of Winlove et al.\textsuperscript{28} showed that one of 5 lysines available per elastin monomer was glycated after 12 days incubation at a sugar concentration 250 mmol/l. Incubation glycation was associated with the appearance of AGE in long-term following. Authors showed that despite the low lysine levels and the consequent low level of glycation cross-links effects on the physical properties of elastin are sufficient to be of a physiological significance. The findings they observed are result of short-term exposure to sugars, and the greater effects could occur in vivo after long-term exposure to glucose.

Non-enzymatic glycation is accelerated in hyperglycaemic conditions but also occurs in nondiabetic state. The process of advanced glycation itself is not harmful, but the products of glycation play a role in vascular injury.\textsuperscript{30} In addition, the rate of accumulation of these end products is related to the severity of the observed complications. This relates to neuropathy, nephropathy, retinopathy and lens disorders for diabetic patients. Although there is increasing evidence for AGEs involvement in the development and progression of diabetic microvascular complications there is a need for definitive and larger human studies to confirm these observations. That is why measurement of serum levels of anti-AGEs antibodies could be important for estimation of an increased risk for development of microvascular complications in diabetic patients.

There is increasing evidence for presence of anti-AGEs antibodies in sera of patients with diabetic microvascular complications. The role of these antibodies in the etiology and pathophysiology of diabetic micro- and macrovascular injury is however yet to be established. In the current study we examined patients with type 2 diabetes mellitus and hypertension. We found that levels of serum anti-AGEs antibodies were significantly higher in diabetics with microvascular complications than healthy controls. Moreover anti-AGEs antibodies levels were higher in patients with microvascular complications compared to patients without such complications. Further examination and prospective studies are needed to clarify whether determination of serum levels of anti-AGEs antibodies might give the possibility for diagnosis and prognosis of the severity of diabetic late complications in hypertonic patients.

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Сывороточные уровни антител к конечным продуктам глубокого гликирования у пациентов с сахарным диабетом 2 типа и гипертонией

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Резюме

Введение и цели: Белки, содержащие конечные продукты глубокого гликирования (AGE), являются высокоиммуногенными, а анти-AGE-антитела обнаруживаются в сыворотке диабетиков.

Материалы и методы: Иммуноферментный анализ (ELISA) использовали для измерения сывороточных уровней анти-AGE-антител у 93 пациентов с сахарным диабетом 2 типа и гипертонией (средний возраст 61.4 ± 11.3 года, продолжительность диабета 9.88 ± 3.12 года, продолжительность гипертонии 9.28 ± 4.98). Эти значения сравнивали с сывороточными анти-AGE-антителами у 42 контролей того же пола и того же возраста. Диабетики были разделены на две группы в зависимости от наличия или отсутствия микроангиопатии, группа 1 (n = 67) и группа 2 (n = 26), соответственно.

Результаты: Сывороточные уровни анти-AGE-антител у пациентов с сахарным диабетом 2 типа и артериальной гипертензией были статистически значимо выше, чем в контрольной группе (1.39 ± 0.39 против 1.05 ± 0.32) (р <0.05). Группа 1 имела статистически значимо более высокие уровни анти-AGE-антител, чем у здоровых контролей (1.53 ± 0.14 против 1.05 ± 0.32) (р <0.01). Уровни анти-AGE антител были выше у пациентов с микрососудистыми осложнениями, чем у пациентов без осложнений. Анти-AGE-антитела коррелировали с диастолическим артериальным давлением (r = 0.26, p = 0.05) и индексом массы тела (r = 0.37, p = 0.03). Мы обнаружили значительно более высокий процент пациентов положительных на анти-AGE-антитела (среднее значение + 2SD) в группе 1, чем в группе 2.

Выводы: Определение сывороточных уровней анти-AGE-антител может помочь врачам поставить ранний диагноз и прогноз поздних осложнений диабета у пациентов с гипертонической болезнью.

Ключевые слова
антитела к продвинутым конечным продуктам гликирования, артериальная гипертония, диабетические микрососудистые осложнения