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ORIGINAL ARTICLE

Circulating Concentrations of Advanced Glycation end Products, its Association With the Development of Diabetes Mellitus

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Background. Diabetes Mellitus (DM) is characterized by the production and accumulation of advanced glycation end products (AGEs), which are one of the key mechanisms in the development of its chronic complications.

Aims of the Study. To assess the serum AGEs concentration by a radioimmunoassay (RIA) developed in our laboratory, to establish reference values in healthy population and to evaluate the diagnostic potential of measuring longitudinal changes in circulating AGEs concentrations to predict the development of DM.

Methods. Clinical and metabolic parameters were obtained from a cohort of 781 Mexican people, initially and then seven years later. AGEs were quantified by a specific RIA. Associations of the changes in circulating levels of AGEs with the appearance of impaired fasting glucose (IFG), and the development of DM were evaluated.

Results. Diabetic subjects had higher circulating levels of AGEs than normoglycemic subjects or individuals with IFG in both samples studied (471 vs. 246 and 342 µU/mL, $p < 0.001$; and 912 vs. 428 and 519 µU/mL, $p < 0.001$; respectively). A multinomial logistic regression analysis showed that subjects who had AGEs concentration ≥400 µU/mL in the baseline sample had a relative risk ratio of 1.98 to develop IFG seven years later ($p = 0.003$). While the subjects who had AGEs concentration ≥450 µU/mL in the baseline sample had a relative risk ratio of 10.7 to develop DM seven years later ($p < 0.001$).

Conclusions. Circulating AGEs concentration is a good early marker to predict risk of developing DM. © 2017 IMSS. Published by Elsevier Inc.

Key Words: AGEs, Insulin resistance, Impaired fasting glucose, Glucose intolerance, Diabetes Mellitus.

Introduction

Advanced glycation end products (AGEs) derived from glucose are molecular structures generated in vivo by prolonged exposure of proteins, lipids, and nucleic acids to chronic hyperglycemic milieus characteristic of poorly

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controlled Diabetes Mellitus (DM). The production and accumulation of AGEs is one of the key mechanisms in the development of chronic complications of DM. Among the mechanisms proposed to induce these structural and functional damages, the modification of enzymes structures which induces alterations in their catalytic ability, the formation of cross-links with proteins of the extracellular matrix, the binding of the AGEs with specific membrane receptors of the RAGE-type initiating a cascade of signaling that induces oxidative stress, as well as the production of proinflammatory cytokines, leading to irreversible damage to tissues and organs such as the kidney, nerves, and microvascular systems, can be mentioned and they cause the appearance of chronic complications (1,2).

Early diagnosis of patients at risk through universal screening could be a strategy to proactively detect deterioration in the metabolic state of the diabetic patients (3). This could contribute to reduce costs of expensive treatments and interventions needed to manage the chronic complications (4). Despite the available scientific information and mostly due to methodological complications, such as the heterogeneity of the AGEs structures formed in vivo, at present, only a few analytical methods to measure different types of AGEs are available. Therefore, in vivo measurements of AGEs have not been performed systematically, standardized, and explored as a potential marker for development and progression of chronic DM complications.

The method most often employed to measure AGEs and generate information on their role and relevance in the pathogenesis of chronic complications of DM, has been the digestion of serum proteins and tissue biopsies, followed by high-performance liquid chromatography combined with fluorescence measurement (5), and immunohistochemistry techniques (6). All these methods are complex and costly, therefore not useful for population screening. We recently developed a radioimmunoassay (RIA), which is a simpler and less costly technique that allows processing large volumes of samples from patients, and that uses a highly specific antibody against AGEs derived from glucose.

The aim of the present study was to measure serum AGEs concentration by our RIA, to establish reference values in healthy population and to evaluate the diagnostic potential of measuring longitudinal changes in circulating AGEs concentrations to predict metabolic changes including the appearance of impaired fasting glucose, and the development of DM in Mexican individuals.

Materials and Methods

Subjects Selection

This study was approved by the Scientific and Ethical Review Committee of the National Institute of Medical Sciences and Nutrition Salvador Zubirán, (key protocol: BRE 557−12/15−1), and included 781 subjects from a cohort of workers of the Social Security Institute in Morelos, Mexico, who met the following inclusion criteria: ≥20 years of age, with a full medical record and complete laboratory data. Initial serum samples (baseline) and those after a seven year period were frozen until assayed. All participants signed the corresponding informed consent form.

Measurements

Anthropometric measurements were performed by a trained staff for this purpose, using a calibrated stadimeter (Seca 206, Hamburg, Germany) and a calibrated scale (Seca 872, Hamburg, Germany). Blood pressure was measured using a WHO approved sphygmomanometer (OMRON HEM-7200, Omron Corporation, Matsusaka, Japan).

Blood samples were collected from subjects who had not performed intense physical activity nor ingested alcohol, after an overnight fasting of at least 12 h and samples were then frozen until assayed. Serum glucose, creatinine, uric acid, total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides were measured by enzymatic colorimetric methods using reagents from Pointe Scientific (Pointe Scientific Inc., Missouri, USA) and an automated biochemical analyzer Mindray BS-200 (Mindray Medical International Limited, Shenzhen, China). Insulin and AGEs derived from glucose were measured by radioimmunoassays (RIA) using a gamma counter Cobra II (Packard Instrument Company, Inc., Connecticut, USA). The index of insulin resistance was estimated by the homeostatic model assessment (HOMA) (7). The estimated glomerular filtration rate (eGFR) was calculated according to Levey *et al* in 2009 (8), and the values adjusted for body surface area (9).

RIA for Insulin

Serum insulin concentration was measured by a RIA previously developed by our working group and carefully validated by comparison of the results with those obtained by the Abbott IMX automated benchtop immunochemistry analyzer (Abbott laboratories, Chicago, USA), which is used to perform measurements of insulin in the diabetes laboratory of our institution. Our method is a competitive radioimmunoassay in liquid phase with precipitation using a second antibody, and a polyclonal antibody produced in guinea pigs against recombinant human insulin (Eli Lilly and Company, Mexico City, Mexico). The RIA has a linearity range from 6.53−209.06 μIU/mL; that in mass concentration corresponds to 0.31−10 ng/mL of insulin standard. This dynamic range allowed for the quantification of serum insulin in both, normoglycemic (NG) control subjects, and in subjects with impaired fasting glucose (IFG) or DM. The method had an intra- and inter-assay precision coefficient of 6.5 and 6.0%, respectively. No interferences with hemoglobin up to 150 mg/dL, bilirubin up to 15 mg/dL, cholesterol up to 668 mg/dL, and triglycerides up to 4192 mg/dL were found.

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