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Original Research

The Investigation of the Oxidative Stress-Related Parameters in Type 2 Diabetes Mellitus

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ABSTRACT

Objective: Oxidative stress, defined as an imbalance between reactive oxygen species production and breakdown by endogenous antioxidants, is closely associated with diabetes mellitus. The diabetes is characterized by hyperglycemia together with biochemical alterations of glucose and lipid peroxidation. Oxidative stress has been implicated in the pathogenesis of type 2 diabetes and its complications.
Methods: This study was conducted to investigate the variation in oxidative stress-related parameters in type 2 diabetes. Blood serum samples were collected from diabetes patients and nondiabetes healthy controls. Glucose concentrations, levels of glycated hemoglobin (A1C) and serum oxidative stress markers (glucose-6-phosphate dehydrogenase [G6PDH], malondialdehyde [MDA], glutathione [GSH], glutathione reductase [GR], glutathione peroxidase [GPx] and superoxide dismutase [SOD]) were estimated.
Results: Fasting serum glucose concentration in type 2 diabetes patients of both sexes was increased significantly as compared with the healthy controls. Level of A1C was greater than standards. Significant elevation in MDA level and depletion in GSH content were observed in diabetes patients in comparison with controls. The diminution in G6PDH activity was accompanied in part by a decrease in the anti-oxidative enzymes activities (GPx and GR), and in part by an increase in SOD activity in all diabetes patients as compared with the control group. The regression analysis showed no correlation between diabetes duration and severity of oxidative stress; however, there was a significant association between A1C and severity of oxidative stress.
Conclusions: The present study shows that there is an oxidative stress state in type 2 diabetes patients compared with healthy subjects. Our data suggest that chronic hyperglycemia causes a significant change in oxidative stress markers.

Mots clés :
glutathion peroxydase
glutathion réductase
malondialdéhyde
stress oxydatif
superoxyde dismutase
diabète de type 2

RÉSUMÉ

Objectif : Le stress oxydatif, qui est défini comme étant le déséquilibre entre la production et l'élimination des espèces réactives de l'oxygène par les antioxydants endogènes, est étroitement associé au diabète sucré. Le diabète est caractérisé par l'hyperglycémie associée aux altérations biochimiques du glucose et à la peroxydation des lipides. Le stress oxydatif a été impliqué dans la pathogenèse du diabète de type 2 et de ses complications.
Méthodes : Cette étude a été réalisée pour évaluer la variation des paramètres du stress oxydatif lié au diabète de type 2. Les échantillons du sérum sanguin ont été prélevés auprès de patients diabétiques et de témoins non diabétiques en santé. Les concentrations de glucose, les taux d'hémoglobine glyquée (A1c) et les marqueurs sériques du stress oxydatif (glucose-6-phosphate déshydrogénase [G6PDH], malondialdéhyde [MDA], glutathion [GSH], glutathion réductase [GR], glutathion peroxydase [GPx] et superoxyde dismutase [SOD]) ont été évalués.
Résultats : La concentration du glucose sérique à jeun chez les patients des 2 sexes ayant le diabète de type 2 a augmenté de manière significative par rapport aux témoins en santé. Le taux d'A1c a été

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supérieur aux normes. Une élévation significative du taux du MDA et une déplétion de la teneur en GSH ont été observées chez les patients diabétiques en comparaison des témoins. La diminution de l'activité de la G6PDH est accompagnée en partie par une diminution des activités des enzymes antioxydantes (GPx et GR) et, en partie par une augmentation de l'activité de la SOD chez tous les patients diabétiques par rapport au groupe témoin. L'analyse de régression ne montre aucune corrélation entre la durée du diabète et la gravité du stress oxydatif. Cependant, il y avait un lien significatif entre l'A1c et la gravité du stress oxydatif.

Conclusions : La présente étude montre qu'il existe un état de stress oxydatif chez les patients ayant le diabète de type 2 par rapport aux sujets en santé. Nos données suggèrent que l'hyperglycémie chronique cause un changement significatif des marqueurs du stress oxydatif.

Introduction

Diabetes mellitus has become a major health problem worldwide in recent times (1). It is widely recognized as one of the leading causes of death and disability (2). There were approximately 194 million adults aged 20 to 79 years with diagnosed diabetes in 2003 (with type 2 diabetes accounting for 90% to 95% of all diagnosed cases) around the world, and that number is expected to increase to 333 million over the next 20 years (3). Diabetes is a chronic disorder of carbohydrate, lipid and protein metabolism (4), and it is characterized by hyperglycemia and insufficiency of secretion or action of endogenous insulin (1,3). The resulting high blood sugar (glycemia) produces the classic symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger) (5). Although the etiology of this disease is not well defined, viral infection, autoimmune disease (3) and numerous genetic and environmental factors have been implicated (3,6).

In 1997, experts from the American Diabetes Association introduced the new classification system used today, abandoning the terms insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus and retaining the terms type 1 diabetes mellitus and type 2 diabetes mellitus (4). Type 2 diabetes is commonly manifested in middle (40 years)-to-late-aged adults; however, its prevalence is increasing in younger populations (5). This disease is a well-known endocrine and metabolic disorder that has reached epidemic proportions worldwide and represents a serious public health concern (7).

Type 2 diabetes is a heterogeneous metabolic disorder defined by the presence of hyperglycemia, which results from a combination of resistance to insulin action and an inadequate compensatory insulin secretion response (8). With type 2 diabetes, patients cannot metabolize carbohydrates, proteins or lipids owing to improper production of insulin, a blood glucose regulator or resistance to insulin. Insulin helps cells use glucose as a main energy source (5). Increased rates of hepatic glucose production result in the development of overt hyperglycemia, especially fasting hyperglycemia. In addition to genetic risk factors for type 2 diabetes, acquired or environmental factors play a major role; foremost among these is obesity (9).

There is a growing scientific and public interest in connecting oxidative stress with a variety of pathological conditions, including diabetes mellitus as well as other human diseases. Previous experimental and clinical studies report that oxidative stress plays a major role in the pathogenesis and development of complications of both types of diabetes (2). Over the past decade, there has been substantial interest in oxidative stress and its potential role in diabetogenesis and the development of diabetes complications (10).

Oxidative stress develops from an imbalance between free radical production, often increased through dysfunctional mitochondria, and reduced antioxidant defences (11,12). The mitochondria electron transport chain is a major source of reactive oxygen species (ROS) in insulin secretion cells, insulin peripheral sensitive cells and endothelial cells (13). Oxidative stress is produced under diabetes conditions and is likely involved in the progression of pancreatic beta-cell dysfunction found in diabetes (14). Hyperglycemia causes tissue damage through 5 major mechanisms: 1) increased flux of glucose and other sugars through the polyol pathway; 2) increased intracellular formation of advanced glycation end products; 3) increased expression of the receptor for advanced glycation endproducts and its activating ligands; 4) activation of protein kinase C isoforms, and 5) overactivity of the hexosamine pathway. Several lines of evidence indicate that all 5 mechanisms are activated by a single upstream event: mitochondrial overproduction of ROS (15).

Oxidative stress has been implicated in the pathogenesis of type 2 diabetes and its complications (16–18). The metabolic disturbances contribute to oxidative stress and compromise the antioxidant defence system in type 2 diabetes patients (19). There seems to be imbalance between oxidant and antioxidant systems in type 2 diabetes patients. These patients are considered to be under oxidative stress because of prolonged exposure to hyperglycemia (20). In view of the above considerations, the present study aimed to evaluate the oxidative status in a group of male and female Algerian patients with type 2 diabetes treated with hypoglycemic agents. Values of glucose, malondialdehyde (MDA) and oxidative stress markers (glucose-6-phosphate dehydrogenase [G6PDH], glutathione [GSH], glutathione reductase [GR], glutathione peroxidase [GPx] and superoxide dismutase [SOD]) in the serum were estimated in comparison with healthy nondiabetes volunteers as controls. Blood percentage of glycated hemoglobin (A1C) was measured, and the body mass index was calculated.

Subjects and Methods

Subjects

This study was conducted with 59 patients with type 2 diabetes who were attending a Diabetes Centre (Annaba, Algeria) for their monthly routine medical examination. There were 34 men (mean age, 47.2±11.4 years) and 25 women (mean age, 48.7±12.0 years). Forty-eight apparently healthy volunteers were also recruited as a control group, 27 men (mean age, 45.1±9.2 years) and 21 women (mean age, 44.2±10.9 years). All subjects were randomly selected and had not been taking any medications other than antidiabetes drugs for the past year (receiving only diabetes treatment). None of the subjects was receiving antioxidant supplementation.

The selection criteria for the subjects were based on a questionnaire. Inclusion criteria were patients with diabetes for at least 5 years, fasting glucose ≥126 mg/dL and levels of glycosylated hemoglobin (A1C) ≥6.5%, in accordance with the World Health Organization (WHO) diagnostic criteria for type 2 diabetes. In our study, normal weight (body mass index <25 kg/m^2) based on the current WHO guidelines is an inclusion criterion to ensure that