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Madrid, España

Available in: http://www.redalyc.org/articulo.oa?id=309224877005
The role of hyperglycemia in the induction of oxidative stress and inflammatory process

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Abstract

Introduction: In many countries, the prevalence of obesity and chronic diseases has been increased, which are normally associated with changes in lifestyle, that are especially characterized by high consumption of diets rich in carbohydrates of rapid absorption. Such diets classified as high glycemic index and high glycemic load can lead to hyperglycemia.

Objectives: Discuss the role of the diets of high glycemic index and/or high glycemic load on the oxidative stress and inflammatory process, in order to verify their influence on those diseases.

Results and discussion: Studies demonstrate direct relationship between hyperglycemia, inflammatory process and oxidative stress that contribute to the development of chronic diseases.

DOI:10.3305/nh.2012.27.5.5917

Key words: Oxidative stress. Inflammation. Hyperglycemia.

Abbreviations

ANOVA: Analysis of variance.
BMI: Body mass index.
CAD: Coronary arterial disease.
CURES: The Chennai Urban Rural Epidemiology Study.
DNA: Deoxyribonucleic acid.
eNOS: Endothelial nitric oxide synthase.
GI: Glycemic index.
GL: Glycemic load.
HDL: High density lipoprotein cholesterol.
HGI: High glycemic index.
HGL: High glycemic load.
ICAM-1: Intercellular-1 adhesion molecule.
IL: Interleukin.
LDL: Low density lipoprotein cholesterol.
LGI: Low glycemic index.
MDA: Malondialdehyde.
NAD+: Nicotinamide adenine dinucleotide.
NADH: Reduced nicotinamide adenine dinucleotide.
NADPH: Nicotinamide adeninedinucleotide phosphate.
NF-κB: Transcription factor nuclear factor-kappa B.
NO: Nitric oxide.
OR: Odds ratio.
PAI-1: Plasminogen activator inhibitor-1.
PCR: Protein C reactive.
ROS: Reactive oxygen species.

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Aceptado: 3-V-2012.

Resumen

Introducción: En muchos países, la prevalencia de la obesidad y las enfermedades crónicas ha aumentado y normalmente se asocia con cambios en el estilo de vida, que se caracteriza sobre todo por el alto consumo de dietas ricas en hidratos de carbono de rápida absorción. Este tipo de dieta clasificada como alto índice glucemico y alta carga glucemica puede llevar a la hiperglycemia.

Objetivos: Discutir el papel de las dietas de alto índice glucemico y/o alta carga glucemica en el estrés oxidativo y en el proceso inflamatorio, a fin de verificar su influencia en las enfermedades.

Resultados y discusión: Los estudios demuestran una relación directa entre la hiperglycemia, el proceso inflamatorio y el estrés oxidativo, que contribuyen al desarrollo de enfermedades crónicas.

DOI:10.3305/nh.2012.27.5.5917

Palabras clave: Estrés oxidativo. Inflamación. Hiperglicemia.
Introduction

Modern life habits are characterized by low energy expenditure daily and by the excessive ingestion of foods rich in carbohydrates and lipids, making the positive energetic balance a reality. The result is the increase of the body mass index (BMI) and the prevalence of obesity, in developed as well as developing countries.

Data from the Survey of Family Budget, made by the Brazilian Institute of Geography and Statistics 2002-2003, revealed that the frequency of overweight and obesity in Brazilians surpasses in eight times the weight deficit among women and fifteen times in males. It was verified, from the 95.5 million people over the age of 20, there are 38.8 million (40.6%) overweight and 10.5 million (10.9%) with obesity. Inadequate eating and excess weight are directly related with the development of chronic diseases. Projections for the next decades indicate an epidemic growth of these diseases in most of the developing countries, specially cardiovascular diseases and type 2 diabetes.

According to the Brazilian Institute of Geography and Statistics data, the national population eat food that have a high content of sugar, especially soft drinks, and a low quantity of fruits and vegetables. This eating pattern characterizes the consumption of a diet with a high glycemic index (HGI) and high glycemic load (HGL). Some authors suggest that the consumption of this type of diet is responsible for the increase of the prevalence of obesity, which might lead to the alteration of the oxidative state and inflammatory markers, besides favoring lipogenesis, hyperglycemia, hyperinsulinemia, reduction of insulin sensibility, hypertriglyceridemia and decrease the concentration of HDL-cholesterol in the blood.

The alteration of the oxidative state seen by the increase in production of reactive oxygen species (ROS) and the reduction of antioxidant concentrations, can be explained by the constant hyperglycemia generated by the chronic consumption of HGI and HGL diets. Furthermore, the hyperinsulinemia associated to insulin resistance can increase the production and release of powerful endothelial vasoconstrictor called endothelin-1, contributing to endothelial cellular injury.

The levels of inflammation markers can predict the development of chronic diseases, aiding in the prevention of future health complications. However, nowadays there are only a few studies that relate the intake of HGI and HGL diets with the referred markers, despite several researches confirming the direct association of these diets with the occurrence of obesity, type 2 diabetes and cardiovascular diseases.

The studies that assess the relation between oxidative stress markers with the consumption of HGI and HGL diets are scarce. Some authors suggest that the oxidative stress can be an early event in the metabolic cascade cause by the ingestion of HGI diets, increasing the risk of cardiovascular diseases and type 2 diabetes.

Therefore, the objective of the present study was to point-out some theoretical references that evaluate the role of consumption of HGI and HGL diets in the oxidative stress and inflammatory process, in order to verify the influence of these types of diets in the predisposition and development of some chronic diseases.

Methods

A bibliographic revision was made evaluating the national and international journals indexed in the scientific data bases Pubmed, Science Direct and Scielo. The descriptors used were: glycemic index, glycemic load, oxidative stress, hyperglycemia, carbohydrate, inflammatory markers, inflammation, inflammation mediators, cardiovascular diseases, chronic diseases and their correspondent in Portuguese. The terms of the research were built combining two or more descriptors or using them isolated.

Articles published between the years 2000 and 2010 were used, approaching the influence of consuming HGI and HGL diets in the oxidative stress and inflammatory process. Relevant articles referenced in the selected studies were also used. The bibliographic research included original and review articles, excluding the studies that evaluated the effects of other interventions, besides diet, in the levels of inflammatory markers and oxidative state. A critical analysis was made of the selected studies to verify the validity of the results obtained.

Oxidative stress and its consequences on chronic diseases

The oxidative stress happens by the overlapping of pro-oxidizing compounds in relation to the antioxidants. This unbalance generates the oxidation of biomolecules with later loss of biological function consequently causing oxidative damages in cells and tissues. The chronic effect of these processes result in relevant implications on the etiology of chronic diseases, for instance, arteriosclerosis, type 2 diabetes, obesity and cancer.

ROS that favor oxidative damage can be comprised of free radicals that contains one odd electron in the electronic layer, such as superoxide, hydroxyl, hydroperoxyl, peroxy, alkoxy, carbonate, carbon dioxide, nitric oxide and nitrogen dioxide and by non-radical reactive species, such, as hydrogen peroxide, hypobromous acid, peroxynitrite and nitrous oxide.

The ROS are formed mainly by the enzymatic complexes nicotinamide adeninedinucleotide phosphate...
(NADPH) oxidases and the endothelial nitric oxide synthase (eNOS). In synthesizing nitric oxide (NO) and the eNOS receives and stores electrons in the reductase, donating NO. Although, the enzyme continuous with the capacity to receive and store electrons in the reductase, donating them to the oxygen substrate. Therefore, the eNOS generates superoxide instead of NO.

The superoxide reacts rapidly with the local NO and forms a reactive species of nitrogen, called peroxynitrite, causing damages in the cellular DNA as well as induces the decoupling of eNOS, which leads to a higher production of superoxide maintaining the conditions of endothelial damage.

The inflamed endothelium expresses that adhesion molecules called selectin and integrins, they activate the adhesion of leucocytes in their surface. Therefore, endothelial dysfunction and consequent atherosclerosis can be triggered by an intermediate accentuated inflammatory response, for example, by oxidation of the low density lipoprotein cholesterol (LDL) which activates the protein kinase C and the transcription factor nuclear factor-kappa B (NF-kB), leading to the increase of conversion enzymes of the angiotensin II, adhesion molecules and inflammatory cytokines.

The relation endothelial-dependent vessel is abnormal in several disease, for instance, type 2 diabetes, heart failure and high blood pressure and they normally associate themselves with the loss of endothelial production and/or bioavailability of NO that trigger in endothelial dysfunction. Furthermore, the endothelial dysfunction can be related to damages of other important functions distinct to vasodilatation, which includes anticoagulation and anti-inflammatory properties of the endothelial.

The determination of the level of oxidative markers is relevance for the early detection of metabolic process that causes the chronic diseases. Therefore, the evaluation of the oxidative stress becomes important to elucidate the mechanisms and biological implications of the oxidative damage. According, there are some methods of analyses, based on the measurement of concentration of molecules resulting from the reaction with the reactive species, by the quantification of the magnitude of the damage produced by the reactive species through the measurement of products of the lipid peroxidation, such as, malondialdehyde (MDA) and F2-isoprostane and by the quantification of the antioxidant capacity.

### Inflammatory responses and its consequences on chronic diseases

A typical inflammatory response occurs from four components: inducers, sensors, mediators and target tissues. The inducers correspond to the factor that triggers the beginning of the inflammatory response; they are detected by sensors, like, the Toll-like receptors (TLRs) which are expressed in specialized sentinel cells, such as, macrophages, dendritic cells and mastocytes that induce the production of mediators, including cytokines (tumour necrosis factor-alfa (TNFα), interleukin-1 (IL-1), interleukin-6 (IL-6), chemokines, bioactive amines, eicosanoids and products of proteolytic cascades, which act like inflammatory mediators in several target-tissue.

The condition of subclinical inflammation state causes lesions in the tissue through the activation of the immune system innate for a long period of time, which can cause future manifestations of chronic diseases, such as, cardiovascular disease, type 2 diabetes, obesity, cancer and metabolic syndrome. The mechanism responsible for the manifestation of these diseases starts with determined specific conditions, such as, abnormally glycosylated protein, high blood pressure, hyperlipidemia, sedentary and abnormal obesity that stimulate the pro-inflammatory mediators (TNFα, interleukins, intercellular-1 adhesion molecule (ICAM-1), vascular-1 cell adhesion molecule (VCAM-1), monocyte chemoattractant protein 1) they trigger insulin resistance, the lack of control in the metabolism of lipids, endothelial dysfunction and oxidative stress, generating the development of the referred chronic diseases.

The acute inflammatory condition can evolve to chronic condition, among these that stand-out in current society, are the inflammatory conditions associated to the diseases mentioned above. In the case of these diseases, it seems to have a vicious cycle between the inflammation and the pathological process.

There are several biomarkers of the inflammatory process that have been used in clinical practice and research associate to diseases, such as, hypertension, type 2 diabetes, arteriosclerosis and obesity. Among them are the adhesion molecules (E-selectin, P-selectin, ICAM-1 and VCAM-1), the interleukins (IL-1β, IL-6), the proteins of acute stage [fibrinogen, serum amyloid protein A, protein C reactive (PCR) ultra-sensitive] and the leukocyte count.

It must be considered that some epidemiological studies have identified the relation between basal levels of TNFα and IL-6 with the increased cardiovascular risk. Adding, Volp et al., in an article review, discussed about several studies that relate IL-6, TNFα and PCR with the occurrence of cardiovascular disease, type 2 diabetes, obesity and metabolic syndrome. Such results indicate that the early detection of specific biomarkers can be predictors of chronic diseases, and therefore, aiding in the prevention of future health complications.
vascular morbidities and mortality of the general population, since the adverse consequences of repeated post-prandial hyperglycemia can build up over a period of several months. Experimental data suggest that the oxidative stress can be an important mechanism that contributes for the relation between acute hyperglycemia and the increase in cardiovascular risk. Acute hyperglycemia can increase the production of free radicals through the non-enzymatic glycosylation and the unbalance of the NADH/NAD⁺ induced by the glucose in cells. Studies made in normal and diabetes subjects showed that hyperglycemia generated in the test of oral tolerance to glucose or after the consumption of meals can induce the oxidative stress and reduce the antioxidant defenses. In diabetic subjects, the increase in oxidative stress was significantly higher after the meals that reproduced a larger increase in glycemia. In vivo studies revealed that the oxidative stress, secondary to glycemia, happens after the later complications of diabetes manifest themselves clinically. This hypothesis is supported by evidence that several biochemical pathways strictly associated to hyperglycemia (autoxidation of glucose, polyol pathway, protein glycation) can increase the production of free radicals (fig. 1).

According to Brownlee (2001) the hyperglycemia leads to mitochondrial superoxide production in endothelial cells and it is implicated in the genesis of complications with diabetes. The superoxide anion binds to the NO, harming its action in the endothelial. Furthermore, the increased production of superoxide activates the protein kinase C, which induced the synthesis of enzyme NADPH oxidase that also contributes to the production of superoxide.

Protein kinase C, a family of enzymes that are involved in controlling the function of other proteins, has been associated to vascular alterations, such as increase of permeability, contraction, synthesis of extracellular matrix, cellular and apoptosis growth, angiogenesis, leukocytes adhesion, activation and inhibition of cytokines. These disturbances in the cell’s vascular homeostasis caused by different isoforms of the protein kinase C (-α, -β₁/₂, -δ) are linked to the development of diseases that affect the large vessels (atherosclerosis, cardiomiopathy) and complications in the small vessels (retinopathy, nephropathy and neuropathy).

Cosentino et al. studied the genetic expression of eNOS and the production of NO in endothelial cells of the human aorta exposed to normal (90 mg/dL) and elevated (396 mg/dL) levels of glucose for five days. This study showed that the prolonged exposure to elevated levels of glucose increases the genetic expression of the eNOS, the expression of protein and the release of NO. However, there is an accentuated increase concomitant from the production of superoxide, a powerful oxidant. These results provide a molecular base for the comprehension of how chronic exposure to elevated levels of glucose lead to unbalance between NO and superoxide.

To elucidate the relation between nutrition and the generation of ROS, Mohanty et al. (2000) evaluated 14 healthy subjects and collected fasting blood samples and 1, 2 and 3 h after the intake of 75 g of glucose. The authors verified that the generation of ROS by polymorphonuclear leukocytes and mononuclear cells increased until reaching a peak of 244 ± 42% and 233 ± 34% of basal levels, respectively, after 2 h. The levels of p47⁺⁺⁺⁺, a key protein in enzyme NADPH oxidase in homogenized mononuclear cells, increased significantly 2 and 3 h after the intake of glucose. The levels of α-tocoferol, an antioxidant, decreased significantly in 1, 2 and 3 h.
Several studies have demonstrated that the hyperglycemia is one of the most important metabolic factors in the development of micro and macrovascular complications in diabetic patients, since the inadequate glycemic control increase the inflammatory activity and the microalbuminuria and favors the endothelial dysfunction, contributing to the predisposition of vascular diseases. Schram et al., in a case-control study with 543 subjects with type 1 diabetics participating in the EURODIAB Prospective Complications Study, verified the glycosylated hemoglobin that reflects the biological activity of the hyperglycemia, was significantly associated with inflammation markers, assessed by means of serum levels of PCR, IL-6 and TNFα.

Mohan et al., evaluated 150 subjects selected from The Chennai Urban Rural Epidemiology Study (CURES), which were divided in 3 groups. Group 1 comprised by non-diabetic subjects without coronary arterial disease (CAD) (n = 50), group 2 comprised by diabetic subjects without CAD (n = 50) and group 3 comprised by diabetic subjects with CAD (n = 50). The diabetic subjects with and without CAD had levels significantly higher of ultra-sensitive PCR (2.89 mg/L and 2.25 mg/L, respectively) when compared with non-diabetic subjects without CAD (0.99 mg/L) (p < 0.001). Values of ultra-sensitive PCR increased with the increase of terciles of body fat and glycosylated hemoglobin (ANOVA p < 0.001). Analysis of multiple logistic regression revealed that the ultra-sensitive PCR was strongly associated with CAD (OR = 1.649, p < 0.05) and diabetes (OR = 2.264, p < 0.01) even after the age and gender adjustments. Therefore, the information mentioned above indicate the direct influence of acute and/or chronic hyperglycemia in the increase of inflammatory activity and oxidative stress.

**Influence of the glycemic index and/or glycemic load of diet in the oxidative stress and inflammatory process**

Considering that the hyperglycemia leads to the increase of risk factors for chronic diseases, several evidences show the influence of the quality and quantity of the dietary carbohydrate in the increase in the incidence of these diseases, especially cardiovascular and type 2 diabetes. This influence of eating in the risk and protection factors related to such diseases is directly related to HGI and HGL diets. In prospective study, it was verified that HGI as well as HGL diets were independent risk factors for cardiovascular events. In another study the association was verified between the consumption of HGI diets with a higher risk for type 2 diabetes, especially in sedentary women and the ones with a familiar history of diabetes.

The concept of GI was introduced in 1981, in order to quantify the post-prandial glycemic response to different foods sources of carbohydrate. The GI clas-
to diets with HGI diet in the oxidative stress and in the risk factors for cardiovascular diseases. It was a crossover study, with 10 days of duration for each stage and interval from 2 to 12 weeks between each stage, both made with subject admitted in clinical research center. Twelve overweight or obese men (27 to 45 kg/m², 18 and 35 years) that consumed LGI or HGI diets were evaluated. Both diets were consumed in the research center and they had the same composition of macronutrients and fibers. In the seventh day of the study, the blood was collected after a night fasting and during 5 hours after having breakfast to assess the total antioxidant capacity (capacity of absorbance of the oxygen radical in plasma) and the level of oxidative stress (urinary F2α-isoprostane). In the tenth day, were measured the cardiovascular risk factors (blood pressure, total cholesterol, HDL-cholesterol, tryglycerols, PAI-1, fibrinogen and PCR). In fasting conditions, the total antioxidant capacity was significantly higher during the consumption of the LGI diet compared with the HGI diet. No effects of diets for the other variables were seen. The increase in total antioxidant capacity of the plasma occurred after a week of ingestion of the LGI diet, before changes occur in other risk factors, increasing the possibility that this phenomenon could mediate, at least in part, the effects previously reported of GI in health.

This study suggests that the changes in total antioxidant capacity comprise in an initial cascade event of metabolic events that relate the GI of the diet to the risk of cardiovascular diseases and diabetes. Furthermore, the intake of HGL diet and low in nutrients diet (specifically with small quantities of antioxidant nutrients) can be harmful to health.

Dickinson et al. evaluated the acute alterations of NF-kB (important mediator of the transcription gene of pro-inflammatory cytokines) after the consumption of two meals with the same composition of macro and micronutrients but differing in the GI. After 10 hours of fasting, 10 healthy eutrophic subjects ingested in separate days 3 meals containing 50 g of carbohydrate available as glucose (HGI), white bread (HGI) and pasta (LGI). Samples of venous blood were collected from fasting (time 0), 1, 2 and 3 hours after the ingestion of the tested meals. Acute changes in other markers of oxidative stress (nitrotyrosine and ICAM-1) were also assessed. The increase in NF-kB was 3 times higher after the ingestion of white bread and glucose compared to the ingestion of pasta (p < 0.05). Similarly, the changes in the levels of nitrotyrosine, but not ICAM-1, were higher after the ingestion of glucose and white bread compared to the pasta (p = 0.01 in 2 hours). The results suggest that the increase in glycemia after the ingestion of meals worsen the inflammatory processes in healthy adults and young people. This mechanism can aid in explaining the relation between carbohydrates, GI and chronic diseases.

Qi et al. also wanted to assess the influence of ingesting whole cereals, brans and fibers to the levels of inflammation markers in diabetic women of the Nurses’ Health Study, furthermore the relation of the GI and GL diet with such markers. The research was made with 902 diabetic women and the food intake was assessed by means of a semi-quantitative food frequency questionnaire. An elevated correlation was seen between the GI diet and concentrations of PCR and TNFα (involved in the genesis of insulin resistance). The concentrations of these inflammation markers were 32% and 11% higher, respectively, in the highest quintile of the GI diet compared with the lowest quintile. Although the women that ingested a HGL diet presented a tendency to higher concentrations of PCR and TNFα, the tendency test were not significant. The ingestion of whole cereals, bran and fiber were associated with values significantly lower of PCR and TNFα. The results highlight the recommendation that patients with type 2 diabetes should increase the ingestion of whole products and maintain a diet with LGI. However, the fact that this study is observational, causality cannot be affirmed. Future research is needed to test the potential benefits of these diet factors in patients with type 2 diabetes.

Similar results were seen by Liu et al. in non-diabetic subjects. The objective of this study was to evaluate if the intake of a HGL diet was associated to elevated concentrations PCR and if this association was modified by BMI. In 244 apparently healthy women, the concentration of plasmatic PCR was measured and the GL diet determined by means of a previously validated semi-quantitative food frequency questionnaire. Through the use of regression models, the association between the GI diet and plasmatic PCR was assessed after adjustments for age, level of physical activity, smoking habits, BMI, family history of heart attack in the myocardium, history of hypertension, diabetes, elevated cholesterol, use of post-menopause hormone, consumption of alcohol and other diet variables.

The authors verifies the occurrence of the positive and strong association and also statistically significant between the GL diet and plasmatic PCR. This association was significantly modified by the BMI. Among women with BMI ≥ 25 kg/m², the concentration of PCR in the lower quintile for GL was 1.6 mg/L and in the higher quintile was 5.0 mg/L. However, among women with BMI < 25 kg/m², the corresponding means were 1.1 and 3.1 mg/L, respectively (p = 0.01 for the interaction). Therefore, the GI diet was significantly and positively associated with the plasmatic concentrations of PCR in healthy middle aged women, independently from other risk factors for ischemic cardiac diseases. This study suggests that the rising of the pro-inflammatory process can be a mechanism in which a consumption of HGI diets increases the risk of ischemic cardiac disease, specifically in overweight women.

Griffith et al. evaluated the relation between GI and GL diet and the levels of ultra-sensitive PCR. During 1 year, 582 men and women that participated of a study
to detect the seasonal variations in the levels of blood lipids, were followed, with visits at the beginning of the study and every 13 weeks, totaling 5 visits per volunteer. No significant associations were seen between the GI and GL diet and levels of PCR. However, it was verified an opposite correlation between GL and PCR among the obese subjects (BMI > 30 kg/m²). These results are surprising for diverging from the ones obtained in other studies and in a previous study led by the same authors, when it was verified that the PCR concentrations were inversely related to the intake of fibers, which is a factor that can affect the GI.

The differences seen in the studies by Liu et al. and Griffith et al. could be explained by the considerably lower PCR values obtained in this study, which could have limited the ability to detect an association between GI or GL and PCR. Due to a limited number of studies on this issue and the conflicting results, future investigations are needed to clarify the effect of the GI/GL in the levels of inflammatory biomarkers, such as PCR.

Conclusion

The oxidative stress and inflammatory process are directly associated to chronic diseases, especially cardiovascular and type 2 diabetes. Among the factors that predispose such conditions we highlight chronic hyperglycemia. Some studies have evidenced that the consumption of HGI and/or HGL diets has as a consequence an rising concentrations of blood glucose and present potential for the triggering of oxidative stress and increase in inflammatory activity, therefore, a possible relation with the future occurrence of chronic diseases.

Due to these consequences, the increase in the intake of HGI and/or HGL diets around the world is concerning. However, to have more scientific support with the intent to warn the population on the harms in adopting these types of diets and the real influence of GI and GL in the oxidative stress and inflammatory process, further study is needed, especially well designed and controlled intervention studies, in which the levels of several types of markers can be analyzed.

References


