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Original Research

Potential Predictive Role of Lipid Peroxidation Markers for Type 2 Diabetes in the Tunisian Population

Houda Bouhajja PhD [a,*], Faten Hadj Kacem MD [a], Rania Abdelhedi PhD [b], Marwa Ncir PhD [c], Jordan D. Dimitrov PhD [d,e], Rim Marrakchi MD [f], Kamel Jamoussi MD [f], Ahmed Rebai PhD [b], Abdelfattah El Feki PhD [c], Mohamed Abid MD [a], Hammadi Ayadi PhD [b], Srini V. Kaveri PhD [d,e], Mouna Mnif-Feki MD [a], Noura Bougacha-Elleuch PhD [g]

[a] *Unit of Obesity and Metabolic Syndrome, Department of Endocrinology, Hedi Chaker Hospital, Sfax, Tunisia*
[b] *Laboratory of Molecular and Cellular Screening Processes, Centre of Biotechnology of Sfax, Tunisia*
[c] *Animal Eco-Physiology Laboratory, Faculty of Sciences of Sfax, Sfax, Tunisia*
[d] *Centre de Recherche des Cordeliers, Sorbonne Universités, Paris, France*
[e] *INSERM, Université Paris Descartes, Paris, France*
[f] *Biochemistry Laboratory, CHU Hedi Chaker, Sfax, Tunisia*
[g] *Laboratory of Molecular and Functional Genetics, Faculty of Sciences of Sfax, University of Sfax, Sfax, Tunisia*

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ABSTRACT

Objectives: We evaluated the potential clinical relevance of malondialdehyde (MDA) and autoantibodies to copper oxidized low-density lipoprotein (CuOx-LDL) in type 2 diabetes occurrence.
Methods: This cross-sectional study enrolled 69 normoglycemic subjects, 18 prediabetic patients and 108 type 2 diabetes patients. MDA concentration was assessed spectrophotometrically. Plasma IgG, IgA and IgM levels to CuOx-LDL were determined by ELISA.
Results: Plasma MDA levels were considerably higher in obese, prediabetic and type 2 diabetes subjects compared to controls. In multiple linear regression analysis, both MDA and IgA to CuOx-LDL were significantly associated with glucose metabolism markers ($p<0.05$). Multiple logistic regression analyses showed that high plasma MDA and IgA to CuOx-LDL were independent risk factors for type 2 diabetes (OR 1.196, 95% CI: 1.058 to 1.353; $p=0.004$; OR 1.626, 95% CI: 1.066 to 2.481; $p=0.024$; respectively). Importantly, elevated IgA to CuOx-LDL predicted incident diabetes in patients with prediabetes (OR 2.321, 95% CI:1.063 to 5.066; $p=0.035$). From stratified analyses by body mass index (BMI), both MDA and IgA to CuOx-LDL remained independent predictors of type 2 diabetes occurrence in non-obese subjects ($p<0.05$). More interesting, elevated IgA to CuOx-LDL levels could be predictors of type 2 diabetes in obese prediabetic subjects ($p=0.044$). Conversely, neither IgG nor IgM to CuOx-LDL was associated with glucose metabolism markers, obesity or type 2 diabetes.
Conclusions: Plasma MDA and IgA to CuOx-LDL were significantly associated with blood markers of glucose metabolism. High levels of MDA and IgA to CuOx-LDL could independently predict type 2 diabetes development in normoglycemia and prediabetic subjects.

Mots clés :
anticorps anti-LDL oxydées
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malondialdéhyde
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RÉSUMÉ

Objectifs : Nous avons évalué la pertinence clinique potentielle du malondialdéhyde (MDA) et des auto-anticorps aux lipoprotéines de faible densité oxydées par le cuivre (CuOx-LDL) dans la survenue du diabète de type 2.
Méthodes : La présente étude transversale comptait 69 sujets non diabétiques, 18 patients prédiabétiques et 108 patients atteints du diabète de type 2. La spectrophotométrie a permis de mesurer la concentration de MDA. La technique ELISA a permis de déterminer les concentrations plasmatiques d'IgG, d'IgA et IgM aux CuOx-LDL.

* Address for correspondence: Houda Bouhajja, PhD, Unit of Obesity and Metabolic Syndrome, Department of Endocrinology, University Hospital Hedi Chaker, El Ain Road, Sfax 3029, Tunisia.
E-mail address: bouhajjahouda@yahoo.fr

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Résultats : Les concentrations plasmatiques de MDA étaient considérablement plus élevées chez les sujets souffrant d'obésité, de prédiabète ou de diabète de type 2 que chez les témoins. À l'analyse de régression linéaire multiple, le MDA et l'IgA aux CuOx-LDL étaient associés de manière significative aux marqueurs du métabolisme du glucose (p<0,05). Les analyses de régression logistique multiple montraient que les concentrations plasmatiques de MDA et d'IgA aux CuOx-LDL étaient des facteurs de risque indépendants du diabète de type 2 (RIA 1,196, IC à 95 % : 1,058 à 1,353; p=0,004; RIA 1,626, IC à 95 % : 1,066 à 2,481; p=0,024; respectivement). Notamment, des concentrations élevées d'IgA aux CuOx-LDL prédisaient l'incidence du diabète chez les patients prédiabétiques (RIA 2,321, IC à 95 % : 1,063 à 5,066; p=0,035). À partir des analyses stratifiées selon l'indice de masse corporelle (IMC), le MDA et l'IgA aux CuOx-LDL demeuraient des prédicteurs indépendants de la survenue du diabète de type 2 chez les sujets ayant un IMC<25 kg² (p=0,003 et p=0,039, respectivement). Plus intéressant encore, des concentrations élevées d'IgA aux CuOx-LDL seraient des prédicteurs du diabète de type 2 chez les sujets prédiabétiques qui avaient un IMC≥25 kg² (p=0,044). À l'inverse, ni l'IgG ni l'IgM aux CuOx-LDL n'était associé aux marqueurs du métabolisme du glucose, de l'obésité ou du diabète de type 2.

Conclusions : Les concentrations plasmatiques de MDA et d'IgA aux CuOx-LDL étaient associées de manière significative aux marqueurs sanguins du métabolisme du glucose. Des concentrations plasmatiques élevées de MDA et d'IgA aux CuOx-LDL seraient respectivement des prédicteurs indépendants du développement du diabète de type 2 chez les sujets ayant une normoglycémie et chez les sujets ayant un prédiabète.

Introduction

The prevalence of type 2 diabetes is growing, so extensive attempts have been made to identify reliable and sensitive biomarkers for the early prediction and diagnosis of type 2 diabetes. Several studies have documented the predictive ability of the anthropometric measures, metabolic and inflammatory markers in discriminating risk for type 2 diabetes (1–3). However, data evaluating the potential clinical relevance of oxidative stress markers in the occurrence of diabetes are lacking.

Elevated lipid peroxidation is well documented in subjects with metabolic syndrome (4), type 2 diabetes (5), impaired glucose tolerance (6) and obesity (7). Lipid oxidation leads to the formation of highly reactive aldehydes with several deleterious effects (8). Malondialdehyde (MDA) is among the most commonly used biomarkers of in vivo peroxidation of polyunsaturated fatty acids. Several previous studies have well documented increased MDA level in subjects with obesity (7) and type 2 diabetes (9,10). A recent data reported the deleterious signalling effect of high MDA level on insulin secretion (11). However, no data has evaluated the MDA value as an independent biomarker of type 2 diabetes.

Oxidative LDL modification has been also shown to be highly immunogenic, leading to OxLDL antibodies formation (12), both in experimental animals and humans (13).These antibodies have shown to predict progression of atherosclerosis, myocardial infarction and coronary artery disease (14,15). However, the predictive role of circulating anti-OxLDL antibodies for type 2 diabetes risk has been less explored. Although IgG anti-OxLDL antibodies are the predominant isotype in humans (16), investigations of its circulating level for their protective or pathogenic role in type 2 diabetes are still controversial (17–20). In addition, very few studies assessed the relationship between plasma IgA to OxLDL and diabetes in humans, where an evidence on positive association of IgA to CuOx-LDL and IgA to malondialdehyde acetaldehyde (MAA)-LDL with type 2 diabetes were reported (17,21). Similarly, data are scarce on the association between circulating IgM antibodies to OxLDL and type 2 diabetes (17). On the other hand, the association of these antibodies with obesity has also been poorly evaluated, with clearly contradictory findings (20–23).

Despite the well documented role of oxidative stress in the pathophysiology of diabetes and its complications, data evaluating the status of oxidative stress in patients at clinical level are scarce. Lipid peroxidation markers have not been regarded as traditional risk factors for type 2 diabetes. Here, we conducted a cross-sectional study to i) evaluate possible association of plasma MDA and OxLDL antibodies levels with obesity and blood markers of glucose metabolism, ii) to investigate the clinical relevance of these lipid peroxidation markers as potential predictive biomarkers to discriminate subjects at higher risk for type 2 diabetes.

Methods

Study population

The study population comprised a sample of 21- to 84-year-old participants (n=195) enrolled in the department of Endocrinology at the Hospital Hedi Chaker (Sfax, Tunisia) in 2012–2014. The study population included 3 groups: group 1 comprised normoglycemic subjects (n=69), group 2 included subjects with prediabetes (n=18) and group 3 comprised type 2 diabetes patients (n=108).The World Health Organization (WHO) criteria were used to diagnose prediabetes and type 2 diabetes as previously detailed (24). The diagnosis of obesity was made according to the WHO standard recommended method (25,26). We excluded participants with cardiovascular diseases, liver and chronic kidney pathologies, thyroid diseases, malignancy, pregnancy, glucocorticoid therapy, acute or chronic inflammatory or infectious disease. The study was approved by the local ethics committee of the Hospital Hedi Chaker of Sfax and all patients were informed.

Anthropometric and biochemical characterization

All participants underwent anthropometric and biochemical characterization. In brief, clinical characteristics including body mass index (BMI), waist circumference (WC), waist to hip ratio and body fat content were recorded for each subject. Blood samples were collected from fasted subjects for the biochemical characterization. Plasma blood glucose, total cholesterol, high density lipoprotein cholesterol (HDL-C), triglycerides (TG), uric acid, creatinine and hepatic enzymes activities were measured using standard clinical methods and an automated chemistry analyzer (ADVIA Siemens 1800 system). Glycated hemoglobin (A1C) was measured using high performance liquid chromatography (HPLC) (Biorad D10). High sensitivity C-reactive protein (hs-CRP) was estimated by nephleometric assay. ELISA method was used to determine both fasting plasma leptin and insulin concentrations according to the commercial suppliers (cat no.: KAP2281 and cat no.: KAP1251, respectively, DIA source Europe S.A.; Nivelles, Belgium).

The HOMA-IR index was calculated as $\text{HOMA-IR} = \text{FPG(mmol/l)} \times \text{FINS}(\mu\text{IU/ml})/22.5$. Insulin sensitivity was evaluated by quantitative insulin sensitivity check index (QUICKI) as follow: