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Original Research

Relationship of Neutrophil-to-Lymphocyte Ratio with Aortic Stiffness in Type 1 Diabetes Mellitus

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ABSTRACT

Objectives: Emerging evidence suggests that the neutrophil-to-lymphocyte ratio (NLR) may be a useful marker of inflammation and aortic stiffness. Markers of inflammation and aortic stiffness are both indicators of cardiovascular events. We, therefore, investigated whether the NLR is associated with aortic stiffness in patients with type 1 diabetes mellitus.
Methods: We examined the relationship of the NLR to aortic stiffness in 76 people with type 1 diabetes and 36 healthy controls.
Results: The NLRs in the group with type 1 diabetes were higher than in the controls (2.33±0.95 vs. 1.80±0.68, respectively; p=0.003). Aortic strain and aortic distensibility, the parameters of aortic stiffness, measured noninvasively by the help of echocardiography, were significantly decreased in the patient group compared to controls (8.0%±1.5% vs. 13.1%±3.3 %; p<0.001 and 3.6±1.1 $cm^2.dyn^{-1}.10^{-3}$ vs. 6.0±2.1 $cm^2.dyn^{-1}.10^{-3}$; p<0.001, respectively). There were negative correlations between NLR and distensibility (r: −0.40; p<0.001) and strain (r: −0.57; p<0.001) in patients with type 1 diabetes.
Conclusions: We have demonstrated that there is a significant negative correlation between the NLR and markers of aortic stiffness in patients with type 1 diabetes, indicating a potential association between inflammation and arterial stiffness. Accordingly, a higher NLR may be a useful additional measure in determining the cardiovascular risks of patients with type 1 diabetes in our clinical practice.

Mots clés :
rigidité aortique
échocardiographie
inflammation
rapport neutrophiles/lymphocytes
diabète sucré de type 1

RÉSUMÉ

Objectifs : De nouvelles données probantes montrent que le rapport neutrophiles/lymphocytes (RNL) peut être un marqueur utile de l'inflammation et de la rigidité aortique. Les marqueurs de l'inflammation et de la rigidité aortique sont tous deux des indicateurs d'événements cardiovasculaires. Par conséquent, nous avons étudié si le RNL est associé à la rigidité aortique chez les patients souffrant du diabète sucré de type 1.
Méthodes : Nous avons examiné la relation entre le RNL et la rigidité aortique chez 76 personnes souffrant du diabète de type 1 et 36 témoins en santé.
Résultats : Le RNL du groupe souffrant du diabète de type 1 était plus élevé que celui du groupe témoin (2,33 ± 0,95 *vs* 1,80 ± 0,68, respectivement; p = 0,003). La déformation aortique et la distensibilité aortique, les paramètres de la rigidité aortique, qui ont été mesurées de manière non effractive à l'aide de l'échocardiographie, avaient significativement diminué dans le groupe de patients comparativement au groupe témoin (8,0 % ± 1,5 % *vs* 13,1 % ± 3,3 %; p < 0,001 et 3,6 ± 1,1 $cm^2.dyn^{-1}.10^{-3}$ *vs* 6,0 ± 2,1 $cm^2.dyn^{-1}.10^{-3}$; p < 0,001, respectivement). Des corrélations négatives étaient observées entre le RNL et la distensibilité (r : −0,40; p < 0,001), puis la déformation (r : −0,57; p < 0,001) chez les patients souffrant de diabète de type 1.
Conclusions : Nous avons démontré qu'une corrélation négative significative existe entre le RNL et les marqueurs de la rigidité aortique chez les patients souffrant du diabète de type 1, ce qui indique une

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association potentielle entre l'inflammation et la rigidité artérielle. Par conséquent, un RNL plus élevé peut être une mesure additionnelle utile dans notre pratique clinique pour déterminer les risques cardiovasculaires des patients souffrant du diabète de type 1.

Introduction

Cardiovascular disease (CVD) is the leading cause of death in people with type 1 diabetes (1,2). In general, the pathogenic mechanism seems to be the destruction of pancreatic beta cells mediated by autoreactive T cells, resulting in chronic insulitis. Thus, chronic inflammation of pancreatic islets plays a pivotal role in the development of the disease (3). Some studies point out that inflammation is likely to play important roles in diabetes-associated cardiovascular events (4). There is increasing evidence that type 1 and type 2 diabetes are associated with enhanced inflammatory states and that inflammatory cells contribute to atherosclerotic lesion initiation and lesion disruption. Higher levels of inflammatory markers, such as C-reactive protein, erythrocyte sedimentation rate and interleukin-6 have been significantly associated with CVD morbidity and mortality (5,6).

Recently, the white blood cell (WBC) count has become a useful predictor of certain diseases as well as a marker of infection. A high-level WBC count, even in the normal range, has been associated with atherosclerotic cardiovascular events (7). Neutrophilia and relative lymphopenia have been shown to be independent predictors of mortality in patients with acute heart failure (8,9). Thus, the neutrophil-to-lymphocyte ratio (NLR) has been proposed as a useful biomarker to predict cardiovascular risk (10–12), and it was introduced as a potential marker to determine inflammation in cardiac and noncardiac disorders (13).

The increased vascular inflammation increases vascular fibrosis and smooth muscle cell proliferation and impairs endothelium-mediated vasodilation, which subsequently results in increased arterial stiffness (AS) (14,15). Increase in AS is an independent risk factor for cardiovascular diseases and mortality (16). AS can be assessed easily by measuring the AS index from the aortic diameters measured by echocardiography and the blood pressure levels obtained by sphygmomanometry (17). Because neutrophil and lymphocyte values are readily available in routine blood count analyses, the NLR may be used as a cost-effective predictor of inflammation and cardiovascular complications.

Despite our knowledge about increased inflammation in patients with type 1 diabetes, the data concerning the NLR and its association with inflammation and AS are lacking in this population. Therefore, we aimed to investigate the relationship between the NLR and AS in patients with type 1 diabetes. Our hypothesis is that the NLR, a novel indicator of inflammation, can be used in patients with type 1 diabetes as a predictor of cardiovascular diseases through aortic stiffness.

Materials and Methods

Patients

Enrolled in this study were 76 patients with type 1 diabetes (38 male and 38 female) with a mean age of 30.6±10.03 years and 36 healthy control subjects (20 male and 16 female) with a mean age of 32.4±8.5 years. The patients who had already been diagnosed as having type 1 diabetes and had been admitted to endocrinology polyclinics for routine controls were selected randomly. Having diabetes was defined as having fasting plasma glucose levels of >126 mg/dL on at least 2 occasions, having spot plasma glucose levels >200 mg/dL with accompanying symptoms of diabetes (polyuria, polydypsia, weight loss) or second-hour plasma glucose levels ≥200 mg/dL during 75 gram oral glucose tolerance tests. Differential diagnoses of type 1 diabetes were made according to the clinical pictures, autoantibodies (antiglutamic acid decarboxylase [antigat] and/or anti-islet) positivity and low serum C peptide levels. All patients were on insulin therapy, and 4 of 76 patients were using angiotensin-converting enzyme inhibitors as antihypertensive drugs.

Clinical and laboratory features of subjects were carefully recorded, including age, gender, body mass index, blood pressure, smoking status, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, high-sensitive C-reactive protein (hsCRPs) and glycated hemoglobin (A1C) levels.

As a control group, we studied 36 individuals without overt cardiovascular disease. They were screened in our outpatient clinic for cardiovascular prevention. Of 36 patients, 2 were using antihypertensive drugs, named as amlodipin and valsartan. Patients and healthy participants were informed about the study protocol, and written consent was obtained from each volunteer. The local ethics board approved the study protocol.

Exclusion criteria

Subjects meeting any of the following criteria were excluded from the study: age older than 60 years to rule out hidden atherosclerosis; WBC counts more than 10×10^3 cells/μL to rule out acute inflammatory disorders; evidence of inflammatory or infectious diseases, malignancies, immunologic or hematologic disorders; treatment with anti-inflammatory drugs; and histories of coronary or structural heart disease.

Laboratory analysis

After a 12-hour overnight fast, blood samples were drawn into plain vacationer tubes from the antecubital veins of subjects. All biochemical analyses, including glucose, creatinine, total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride concentrations were performed with an oxidase-based technique in our central biochemistry laboratory. A1C levels were measured by the high-performance liquid chromatography method. The hsCRP was measured using a latex-enhanced immunoturbidimetric method with lower limits of detection at 0.02 (mg/L). Complete blood counts with automated differential counts, which included total WBCs, neutrophils and lymphocytes, were obtained at the time of admission. The NLRs were calculated as the ratio of the neutrophil and lymphocyte counts.

Evaluation of arterial stiffness

Echocardiography was used to assess arterial stiffness. Echocardiographic evaluations of patients with diabetes and control group were made by a cardiology expert, who was blinded to clinical and laboratory findings. Echocardiographic examinations were obtained by using a 2.5 to 3.5 MHz transducer with Vingmed System 7 (Vivid 7, GE; Horten, Norway) equipment. M-mode echocardiography and quantitative analyses were conducted on