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Original article

Impact of diabetes on neutrophil-to-lymphocyte ratio and its relationship to coronary artery disease

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Abstract

Background. – Coronary artery disease (CAD) is the leading cause of mortality among diabetic patients, and the neutrophil-to-lymphocyte ratio (NLR) has recently emerged from among inflammatory parameters as a potential indicator of vascular complications and poorer outcome in patients with diabetes. This study aimed to evaluate: 1) the impact of diabetes on NLR; and 2) the role of NLR on the extent of CAD among diabetic patients undergoing coronary angiography.

Methods. – Consecutive patients undergoing coronary angiography were included. Diabetic status and main chemistry parameters were assessed at the time of admission. Significant CAD was defined as at least one vessel with stenosis > 50%, while severe CAD was left main and/or three-vessel disease, as evaluated by quantitative coronary angiography (QCA).

Results. – Diabetes was observed in 1377 of 3756 patients (36.7%); they were older, and displayed higher-risk cardiovascular profile and more complex CAD. Diabetic status was also associated with a significant increase in NLR ($P = 0.004$). Among diabetics, higher NLR tertile values were related to ageing ($P < 0.001$), dyslipidaemia ($P < 0.001$), renal failure ($P < 0.001$), body mass index ($P < 0.001$), previous percutaneous coronary revascularization ($P = 0.004$) and cerebrovascular events ($P = 0.003$), acute presentation ($P < 0.001$), treatment at admission with beta-blockers/statins/ASA (all $P < 0.001$), diuretics ($P = 0.01$) or clopidogrel ($P = 0.04$), platelet count ($P = 0.03$), white blood cell count, creatinine, glycaemia and C-reactive protein ($P < 0.001$), and inversely related to haemoglobin, triglyceride levels ($P < 0.001$) and smoking ($P = 0.03$). NLR was associated with multivessel disease ($P < 0.001$), degree of stenosis ($P = 0.01$), type C lesions ($P = 0.02$), coronary calcifications and intracoronary thrombus ($P < 0.001$), but inversely with in-stent restenosis ($P = 0.003$) and TIMI flow grade ($P = 0.02$). Also, NLR was directly related to CAD prevalence ($P < 0.001$; adjusted OR [95% CI]: 1.62 [1.27–2.07], $P < 0.001$) and CAD severity ($P < 0.001$; adjusted OR [95% CI]: 1.19 [1.00–1.43], $P = 0.05$).

Conclusion. – NLR is increased among diabetic patients and, in such patients, is independently associated with the prevalence and severity of CAD. Further studies are now needed to confirm present results and to evaluate the underlying pathophysiological mechanisms behind our findings.

Keywords: White blood cells; Neutrophils; Lymphocytes; Diabetes mellitus; Coronary artery disease

1. Introduction

Various efforts have been made in the last few years to deal with the diabetes 'epidemic', and to treat and prevent coronary artery disease (CAD) among these patients [1,2]. However, despite the introduction of more potent antiplatelet agents and

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new techniques for percutaneous revascularization, the results have, so far, proven unsatisfactory, with diabetic patients still experiencing a higher rate of cardiovascular events and poorer outcomes, especially in the setting of acute coronary syndromes [3–5]. For this reason, considerable attention has been directed towards the identification of new markers of cardiovascular risk in such patients [6,7].

Chronic inflammation plays a central role in the development and progression of diabetes, and in the pathogenesis of its complications [8]. In particular, white blood cells are leading actors in the processes of vascular wall degeneration in patients with diabetes, being involved in the evolution of atherosclerosis and in the destabilization and rupture of plaque, resulting in thrombotic events [9,10].

Moreover, growing interest has been directed towards leukocyte subtypes and especially the neutrophil-to-lymphocyte ratio (NLR), an inexpensive and convenient way to identify inflammatory parameters, and potentially an even more accurate indicator of cardiovascular risk than absolute blood cell counts [11,12].

However, until now, few reports have evaluated the relationship between diabetes and NLR and its impact on CAD in diabetic patients, this was the aim of the present study.

2. Methods

Our study population comprised consecutive patients undergoing coronary angiography between April 2007 and December 2013 at the Ospedale Maggiore della Carità in Novara, Italy. Informed consent was obtained from all patients before angiography, and the study protocol was approved by the Local Ethics Committee. All demographic and clinical data were prospectively collected in a dedicated database. Hypertension was defined as a systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg or if the individual was taking antihypertensive medication. Diabetes was defined as a previous diagnosis, specific treatment administration (oral antidiabetic drugs or insulin), fasting glycaemia > 126 mg/dL or HbA_{1c} > 6.5% [13]. Chronic renal failure was considered in those with a history of renal failure or an admisson glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2, as defined by the Modification of Diet in Renal Disease (MDRD) study. Acute coronary syndrome at admission was defined as chest pain lasting more than 10 min, associated with elevation of cardiac biomarkers beyond the upper limit of normal (ULN; 0.04 μg/L for troponin I and 5.00 μg/L for creatine kinase [CK]-MB), with or without changes on electrocardiography (ECG) [14].

2.1. Biochemical measurements

Blood samples were drawn (following a fasting period of 12 h) at admission in patients undergoing either elective or emergency coronary angiography. Glucose, creatinine, glycosylated haemoglobin (HbA_{1c}) and lipid profiles were determined by standard methods.

The white blood cell (WBC) count was measured in a blood sample collected in tripotassium (K3) EDTA (7.2 mg) tubes and analyzed within 2 h of venepuncture by an automatic blood counter (XE-2100, Sysmex Corporation, Kobe, Japan) [15].

2.2. Coronary angiography

Coronary angiography with a digital system (AXIOM Artis dTC, Siemens Medical Solutions, Erlangen, Germany) was routinely performed, using the Judkins technique and 6-Fr right- and left-heart catheters. Quantitative coronary angiography (QCA) was performed using an automatic edge-detection system (QuantCor QCA with ACOM, Siemens), as described elsewhere [16]. The measured parameters were minimal luminal diameter, reference diameter, percent diameter stenosis and length of lesion. Significant CAD was defined as the presence of at least one coronary vessel stenosis > 50%, while severe CAD was defined as three-vessel disease and/or left main disease. In cases where patients had previously undergone a percutaneous coronary intervention (PCI), even though no restenosis was observed, the treated vessel was counted as significant disease. In previous heart-bypass patients, native arteries and grafts were taken into account when evaluating the extent of arterial disease (number of diseased vessels).

2.3. Study endpoints

These were:

- evaluation of the impact of diabetes on NLR;
- evaluation of the association between NLR and the extent of CAD in diabetic patients.

2.4. Statistical analysis

Statistical analysis was performed using SPSS version 15.0 software. Continuous data were expressed as mean ± SD, and categorical data as percentages. Analysis of variance (ANOVA) and the chi-square test were used for continuous and categorical variables, respectively. Diabetic patients were grouped according to tertiles of NLR, and linear regression analysis was used to evaluate the relationship of NLR to glycaemic status. Binary multiple logistic regression was performed to evaluate the relationship between NLR and CAD after correction for baseline confounding factors (all variables displaying a significant P value on univariate analysis), which were entered into the model as a block. $P < 0.05$ was considered statistically significant.

3. Results

The study population included 3756 subjects undergoing coronary angiography. Among them, 1377 (36.7%) had diabetes. Table 1 shows the main clinical and demographic features of the study population according to diabetic status, which was related to ageing, hypertension, higher body mass index (BMI) scores, dyslipidaemia, renal failure, history of myocardial infarction, percutaneous and surgical coronary revascularization, cerebrovascular accidents, and treatment at admission with