The Relationship between Neutrophil-to-Lymphocyte Ratio and Intracerebral Hemorrhage in Type 2 Diabetes Mellitus

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Introduction: Chronic systematic inflammation has been suggested to be associated with the occurrence and development of cardiovascular events. Low-grade systematic inflammation persists in type 2 diabetes mellitus (T2DM) patients. In addition, the risk of cerebral hemorrhage in these patients is increased compared with non-diabetic patients. Neutrophil-to-lymphocyte ratio (NLR) is the ratio derived by dividing the neutrophil count with the lymphocyte count from a peripheral blood sample. This study aimed to explore the relation between NLR and cerebral hemorrhage, and to prove that NLR is an independent risk factor of cerebral hemorrhage in T2DM patients. *Methods:* In total, 429 cases of T2DM patients were included. The patients were divided into two groups depending on the presence of cerebral hemorrhage: the cerebral hemorrhage group (n = 87) and the control group (n = 342). Based on clinical and laboratory data of diabetes diagnosis, this article investigates the relationship between NLR and the risk of cerebral hemorrhage. *Results:* Increase in NLR was positively correlated with the incidence of cerebral hemorrhage in T2DM patients and might serve as an independent risk factor of cerebral hemorrhage in T2DM patients (OR: 4.451, 95% CI: 2.582-7.672). NLR >2.58 might be useful in predicting the threshold value of cerebral hemorrhage risk in newly diagnosed T2DM patients (area under the curve: .72, 95% CI: .659-.780, $P < .001$) *Conclusion:* As an indicator of the degree of systematic inflammation, NLR is an independent risk factor of cerebral hemorrhage in T2DM patients. **Key Words:** Intracerebral hemorrhage—type 2 diabetes mellitus—neutrophil-to-lymphocyte ratio—inflammation.

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Statement of human and animal rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Statement of informed consent: Informed consent was obtained from all patients for being included in the study.

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Introduction

As a common metabolic disease, type 2 diabetes mellitus (T2DM) is complicated by many cardiovascular diseases and cerebrovascular diseases, such as peripheral vascular diseases, heart failure, and intracerebral hemorrhage (ICH).[1,2] Compared with non-diabetic patients, diabetic patients are at a higher risk of hemorrhagic stroke.[2] ICH can cause considerable damage to the central nervous system, with a high rate of disability and mortality.[3] Thus, the risk factors and pathogenesis of ICH in T2DM patients attract increasing attention.

The mechanism of ICH in T2DM remains unclear. However, studies have demonstrated that the risk of ICH is increased with chronic inflammation[4] and that diabetic patients exhibit long-term chronic inflammation.[5,6] It is easy and effective to obtain the neutrophil-to-lymphocyte ratio (NLR), an index of systemic inflammation.[7] Its prognostic value in tumors[8] or cardiovascular diseases[9] has been suggested by recent studies. Its association with diabetic complications has gradually received attention.[10-13] Elevated NLR is associated with risk factors of ICH, including atherosclerosis[14] and hypertension.[15] Therefore, elevated NLR itself may be used as an alternative marker to predict the pathogenesis of ICH. The present study was designed to explore the correlation between NLR and ICH in T2DM patients and the independent risk factors of ICH in T2DM patients. This information will assist patients in taking early precautions to reduce the impact of ICH on both the health and wealth of T2DM patients.

Methods

Subjects

All procedures were in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2008. The local ethics committees approved the study protocol. In this study, 1259 diabetes patients admitted to Zhujiang Hospital and Chinese PLA General Hospital between January 2008 and December 2014 for their primary diseases were retrospectively evaluated using the electronic medical record system. Of these patients, 848 were newly diagnosed with T2DM and were included for further exclusion. T2DM was diagnosed based on the American Diabetes Association consulting criteria (i.e., fasting plasma glucose [FPG] of ≥7.0 mmol/L [126 mg/dL] or a 2-hour postglucose value of ≥11.1 mmol/L [200 mg/dL]).

Of these 848 patients, patients who matched the following exclusion criteria were excluded: cardiovascular diseases, myocardial infarction, heart failure, active infection, active massive hemorrhage, acute poisoning, cancer or blood diseases that affect the neutrophils or lymphocytes (e.g., myeloproliferative diseases and leukemia), ICH before admission or caused by other confirmed reasons after discharge (trauma, drugs, congenital abnormalities, coagulation disorders, vasculitis, brain tumor, vascular amyloidosis, or hemorrhage secondary to ischemic stroke), or taking medication that affects the neutrophils and lymphocytes (chemotherapy or radiotherapy to malignancy, granulocyte colony stimulating factor therapy, or corticosteroid therapy).

After the second exclusion, 429 patients were included. Phone follow-up was implemented by using the patient database of Zhujiang Hospital and Chinese PLA General Hospital. Regarding the 75 patients who were diagnosed with ICH at Zhujiang Hospital and Chinese PLA General Hospital and 12 patients who were diagnosed with ICH at other hospitals, the patients or their family members were required to return to the hospital for a follow-up visit and information supplement. All 87 ICH patients were categorized into the ICH group. In total, 342 patients whose age and gender matched the criteria were categorized into the control group.

We followed the American Diabetes Association guidelines[16] to treat T2DM and The American Heart Association/American Stroke Association guidelines[17] to treat ICH. For other complications, patients were provided standard symptomatic treatment.

Data Collection

After a minimum 8-hour fasting, the systolic and diastolic pressure of all patients were measured by standardized mercury sphygmomanometer (XJ11D, Shanghai Medical Instruments Co., Shanghai, China). The height and weight were also measured to calculate the body mass index as weight divided by height squared (kg/m^2). Venous blood sample was obtained from the ulnar vein of each patient after clinical measurements of blood pressure, height, and weight. Laboratory tests, including hemoglobin A1c (HbA1c), fasting glucose, fasting insulin, creatinine, uric acid, triglyceride, total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL), were conducted.

The daily urine of each patient was collected to measure urinary microalbumin using a turbidimetric immunoassay (Wako Pure Chemical Industries, Ltd, Osaka, Japan). Fasting glucose was measured using the glucose oxidase method. Fasting insulin was measured by the chemiluminescence method. An automated biochemical analyzer Synchron CX5 (Beckman Instruments Inc., Brea, CA) was used to measure the triglyceride, total cholesterol, HDL, and LDL. HbA1c was measured using an automated high-performance lipid chromatography Tosoh G7 (Tosoh Europe N.V, Tessenderlo, Belgium). Insulin resistance (IR) was assessed with a homeostasis model. Homeostasis model of assessment for insulin resistance index is FPG (mmol/L) × FIN (mU/L)/22.5.[18]

Definitions

ICH was defined as a stroke for which computed tomography scanning can identify an area of high density within the brain parenchyma with or without extension