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Relation between Neutrophil to lymphocyte ratio in diabetic patients and severity of ischemic heart disease

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Abstract: Type 2 diabetes (T2D) is a major global health problem that affects more than 285 million individuals worldwide. It alters components of the immune system and is associated with elevated levels of the inflammatory markers as interleukin 6 (IL6) and C-reactive protein (CRP) and in particular Neutrophil: lymphocyte ratio (NLR) which corresponds to numerous chronic inflammatory diseases. NLR is being related to arterial stiffness and high coronary calcium scores, which are significant markers of CVD. Inflammatory cells contribute to atherosclerotic lesion initiation and lesion disruption, which could cause acute coronary syndrome and other cardiovascular events. NLR is calculated as a simple ratio of the absolute neutrophil count to the absolute lymphocyte count. It was defined as a potential biomarker of inflammation in cardiovascular conditions, diabetes and its complications. Higher level of NLR is related to a higher severity of coronary artery disease and worsen clinical outcome in patients undergoing percutaneous coronary intervention (PCI).
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Introduction

Type 2 diabetes (T2D) is a major global health problem that affects more than 285 million individuals worldwide (1), and it has reached epidemic proportions in China. An estimated 92.4 million adults age 20 years or older (9.7% of the adult population) have diabetes, and 60.7% of these cases are undiagnosed (2). Another 148.2 million adults (15.5%) have pre-diabetes, which is an important risk factor for the development of overt diabetes as well as cardiovascular disease (CVD) (3, 4). The increasing burden of T2D (5) demonstrates an immediate need for elucidating the mechanisms that underlie its pathophysiology of in order to implement preventative strategies.

Prior studies have indicated that components of the immune system are altered in obesity and T2D (6) and that elevated levels of the inflammatory markers interleukin 6 (IL6) and C-reactive protein (CRP) are associated with the development of T2D (7). Other research has indicated that inflammation of pancreatic islets can reduce insulin secretion and trigger β-cell apoptosis (8). This led us to hypothesize that immune markers might be useful predictors of T2D.

NLR as an inflammatory marker:

Neutrophil: lymphocyte ratio (NLR), which has become one of the most popular biomarkers in biological and medical research in recent years, has been shown to correspond to numerous chronic inflammatory diseases (9, 10). NLR is both accessible and affordable, and it thus has been increasingly used in clinical trials and research studies; however, few studies have examined the relationship between NLR and T2D (11).

NLR reflects both the lymphocyte and neutrophil counts. The power of NLR as an inflammatory factor stems from both a reduction in the lymphocyte count and an increase in the neutrophil count. Tanaka *et al*. (12) showed that T lymphocytes were reduced in obese people and that lymphopenia appeared to be related to inflammation through TNFα. Neutrophils are the first immune cells to respond to inflammation and can exacerbate the chronic inflammatory state by helping recruit macrophages and by interacting with antigen-presenting cells. An animal study demonstrated that neutrophil elastase could degrade the insulin receptor substrate 1 and reduce insulin-induced Akt phosphorylation in adipocytes. This mechanism may be involved in the neutrophil effect on insulin resistance (13).

Several studies have established the utility of NLR as a medically relevant biomarker. NLR can single out individuals that are at risk for sensorineural hearing loss (caused by vascular complications of diabetes via inflammation) (14) or those that are at risk for adverse cardiac events (15). One review article also indicated that NLR has been related to arterial stiffness and high coronary calcium scores, which are significant markers of CVD (16). Recently, NLR has been reported to be a prognostic marker for outcomes

that result from diabetic retinopathy (17), including microvascular complications (18) and impaired renal function (19). Although the precise mechanisms that underlie the associations between systemic inflammation and prevalent conditions remain to be elucidated, these studies verify the present conclusion that NLR could be used as an innovative and effective predictor for T2D.

Inflammation and severity of atherosclerosis:

Inflammation can be a cause of numerous diabetic complications that represent a complex set of phenomena that stretch beyond the field of inflammation proper. Corvera et al. (20) proposed that during diabetic complications, the early formation of advanced glycation end products associated with hyperglycemia stimulates mechanisms that lead to the recruitment of key components of the inflammatory response. Indeed, studies have shown that the advanced glycation end products receptor-mediated regulation of adiposity and inflammation may result in T2D and diabetic vascular complications (21). Other research has shown that serum levels of IL6, IL17, interferon γ, TNFγ, IL2, and IL10 were increased in T2D nephropathy (T2DN) patients (22), and inflammatory responses (such as increased expression of toll-like receptors) were involved in the perpetuation of inflammation in the diabetic kidney (23). During the development and progression of T2DN, increased oxidative stress leads to the activation of the poly (ADP-ribose) polymerase pathway, which regulates the expression of genes that are involved in promoting inflammatory reactions (24). A study by Vinik *et al*. (25) emphasized that a loss of heart rate variability, which occurs early in the development of autonomic dysfunction, correlates with an increase in circulating inflammation markers, such as CRP and IL6. Collectively and combined with the present findings, these results suggest that inflammation likely contributes to the pathophysiology of and complications that result from T2D.

Type 2 diabetes also increases the risk of atherosclerosis/cardiovascular disease two- to fivefold (26). Carotid artery intima-media thickness (cIMT), which serves as a well- established biomarker of subclinical atherosclerosis, is a risk factor for cardiovascular disease and can be used to predict cardiovascular events (27,28); it is significantly greater in patients with type 2 diabetes than that in non-diabetes subjects (29).

Some studies have pointed out that inflammation plays an important role in diabetes and its chronic complications, and is also associated with cardiovascular events (30-32). Inflammatory cells contribute to atherosclerotic lesion initiation and lesion disruption, which could cause acute coronary syndrome and other cardiovascular events. Several inflammatory markers (such as fibrinogen, C- reactive protein [CRP], interluekin-18 and tumor necrosis factor- a), which are associated with markers of asymptomatic atherosclerosis in type 2 diabetes (33), are difficult to obtain in common clinical practice. Therefore, simpler and more convenient markers are required.

Mounting evidence has shown that the white blood cell (WBC) count and its subtypes are classic indicators of inflammation (34). The neutrophil-to-lymphocyte ratio (NLR) was calculated as a simple ratio of the absolute neutrophil count to the absolute lymphocyte count. It was defined as a potential biomarker of inflammation in tumors (35-37), cardiovascular conditions (38,39), and diabetes and its complications (40,41). Previous studies have shown that a higher level of NLR was related to a higher severity of coronary artery disease and worse clinical outcome in patients undergoing percutaneous coronary intervention (42-45). Akbasetal. (18) reported that the level of NLR was significantly higher in diabetic nephropathy patients with albuminuria. Uluetal. (46) also reported a positive correlation between the NLR and different diabetic retinopathy grades.

The exact mechanisms of the higher level of NLR being associated with diabetes and its complications are still unclear, and the most important mechanism might be inflammation. However, the relationship between diabetic cIMT and NLR has not been investigated to date. The objective of the present study was to investigate the role of NLR in cIMT development among type 2 diabetes patients.

Conclusion:

NLR is increased as inflammatory marker in diabetic patients and, in those patients, this is independently associated with advanced atherosclerosis and both the prevalence and severity of Coronary artery disease.

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