Neutrophil-lymphocyte ratio correlates with limited joint mobility of hand in patients with type 2 diabetes

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Abstract. Limited joint mobility (LJM) of hand, which is one of the complications of diabetic hand, is associated with diabetic micro- and macroangiopathy although the precise pathogenesis is not completely understood. Neutrophil-lymphocyte ratio (NLR), a simple and novel inflammatory marker, has been reported to have a predictive effect to some diabetic complications in recent years. However, it is not elucidated about the relationship between LJM of hand and NLR in patients with type 2 diabetes. We evaluated the relationships between LJM of hand and NLR in 335 consecutive patients with type 2 diabetes in this cross-sectional study. LJM of hand was diagnosed by a 'prayer sign' or 'table test'. LJM of hand was present in 80 patients. The patients with LJM of hand had significantly older age, longer duration of diabetes, worse renal function, and higher proportion of diabetic neuropathy, retinopathy and nephropathy. NLR in patients with LJM of hand was higher than that in patients without LJM of hand (2.54 ± 1.46 vs. 2.11 ± 1.04 , $p = 0.004$). Multivariate logistic regression analysis revealed that LJM of hand was positively correlated with NLR (odds ratio, 1.31; 95% confidence interval 1.03–1.69, $p = 0.027$) after adjustment for age, sex, duration of diabetes, body mass index, hemoglobin A1c, hypertension and dyslipidemia. Our results demonstrate a positive relation between LJM of hand and NLR in patients with type 2 diabetes.

Key words: Clinical practice, Neutrophil-lymphocyte ratio, Diabetic hand, Limited joint mobility

'DIABETIC HAND', which manifests as conditions such as limited joint mobility (LJM), Dupuytren's contracture and trigger finger, is a complication of the upper extremity in patients with diabetes [1-5]. Diabetic hand tends to be ignored in clinical situations [6] in spite of several studies reporting the association between LJM of hand and micro- [1-4, 7] and macroangiopathy [8, 9]. The precise etiology of LJM of hand is not completely understood although multi-factorial reasons were hypothesized such as a genetic component, increased non-enzymatic collagen glycosylation and polyol pathway due to chronic hyperglycemia [4, 5, 10].

Type 2 diabetes mellitus is thought to be an inflamma-

tory disease triggered by disordered metabolism [11]. Hyperglycemia and micro-inflammation are considered to be related to diabetes and its complications [12]. A raised white blood cell (WBC) is reported to be associated with higher risk of type 2 diabetes [13]. Neutrophils indicate the active nonspecific inflammatory mediator, which leads to ischemic injury [14], whereas lymphocytes indicate the protective component of inflammation [15].

Neutrophil-lymphocyte ratio (NLR), which can be calculated easily using peripheral blood count, has a close association with inflammation, which related to cancer and cardiovascular disease [16-18]. In addition, it has also been reported that NLR is associated with insulin resistance [19] and diabetic retinopathy and nephropathy [20, 21]. However, to our best of knowledge, there are no reports about the relationship between NLR and diabetic hand in patients with type 2 diabetes. Therefore, we investigated the relationship between NLR and LJM of hand in this cross-sectional study.

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Research Design and Methods

Study design and patients

This study was conducted in accordance with the Declaration of Helsinki and informed consent was obtained from all patients. Ethics Committee of Otsu Municipal Hospital gave approval for this study. In this study, we included the patients who were examined the LJM of hand, from April 2012 to December 2014 at outpatient clinic of Otsu Municipal Hospital. Patients with a history of articular rheumatism or surgery for spinal disease were excluded. Patients with acute inflammatory or infectious disease, severe tissue damage, acute massive hemorrhage, malignancies or hematologic diseases which affect neutrophils and lymphocytes, were also excluded.

All patients provided details of their demographics and medical history. According to self administered questionnaire, patients were classified as current smokers or not. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Type 2 diabetes was diagnosed according to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [22].

Neuropathy was defined using the diagnostic criteria for diabetic neuropathy proposed by the Diagnostic Neuropathy Study Group [23]. Diabetic neuropathy was diagnosed as follows: neuropathic symptoms such as decreased or absent ankle reflex (bilateral); neuropathic pain, paresthesia and numbness and decreased distal sensation assessed by C128 Hz tuning fork without evident non-diabetic peripheral neuropathy.

Retinopathy was assessed by ophthalmologists blinded to the severity of other diabetic complications and was graded as proliferative diabetic retinopathy (PDR) or non-PDR according to the International Clinical Diabetic Retinopathy Disease Severity Scale [24]. If findings in the left and right fundi were discordant, the worse side was taken as representative of the patient. Nephropathy was graded as normoalbuminuria, urine albumin excretion (UAE) <30 mg/g creatinine (Cr); microalbuminuria, 30–300 mg/g Cr; or macroalbuminuria, >300 mg/g Cr [25]. Microalbuminuria and macroalbuminuria were considered to indicate nephropathy.

LJM of hand was objectively recorded and diagnosed using a ‘prayer sign’ or ‘table test’, which is commonly used for assessment of LJM. We asked the patients to close their palms in a praying position with the fingers in contact with each other or to place the palms on a table

with the wrists flexed maximally. Patients with LJM of hand are unable to bring the palms together or place them on a table with full contact [2–4].

Data collection and measurements

Blood samples were drawn in the morning after an overnight fast for measurement of blood count (including neutrophil and lymphocytes), glycated hemoglobin (HbA1c), total cholesterol (TC), triglycerides (TG), uric acid (UA) and creatinine. Complete blood count and examinations were performed using a Beckman Coulter LH 780 instrument and Bio Majesty JCA-BM 6050 (JEOL, Tokyo, Japan).

NLRs were calculated as the ratio of the absolute neutrophil and lymphocyte counts. Total white blood cells (WBCs), neutrophils and lymphocytes, were obtained from the same automated blood sample. Hypertension was defined as systolic blood pressure (SBP) >140 mmHg, diastolic blood pressure (DBP) >90 mmHg, and/or having received treatment for hypertension. Dyslipidemia was defined as a TC concentration >5.69 mmol/L, a TG concentration >1.70 mmol/L, and/or having received treatment for dyslipidemia.

The estimated glomerular filtration rate (eGFR) was used to estimate kidney function and was calculated as follows [26]: Male: $\text{eGFR (mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}) = 0.741 \times 175 \times \text{age}^{-0.203} \times (\text{serum creatinine})^{-1.154}$. Female: $\text{eGFR} = 0.741 \times 175 \times \text{age}^{-0.203} \times (\text{serum creatinine})^{-1.154} \times 0.742$.

Statistical analysis

Statistical analyses were performed using JMP v. 9.0 (SAS Institute Inc., Cary, NC). A *p* value <0.05 was considered significant. Continuous variables were presented as the mean value $\pm$ 1 SD. Categorical variables were presented as a number (percentage).

The significance of differences between groups was evaluated by unpaired Student *t*-test or Pearson χ^2 test. Pearson’s correlation analyses were used to assess the relationships between NLR and the other variables. Univariate and multivariate logistic regression analyses were used to investigate the relationship between LJM of hand and NLR. In multivariate logistic regression analysis, factors which were found the association in univariate analysis and which had been known the association with diabetic hand, were selected for covariates; age, sex, duration of diabetes, BMI, HbA1c, hypertension, and dyslipidemia.

Results

LJM was examined in 416 consecutive patients with type 2 diabetes. Of these patients, 81 were excluded because of histories of rheumatoid arthritis or surgery for spinal disease ($N = 40$), acute inflammatory or infectious disease ($N = 3$), severe tissue damage ($N = 12$), acute massive hemorrhage ($N = 2$), and malignancies or hematologic diseases ($N = 24$). A total of 335 patients with type 2 diabetes were included in this study. The clinical characteristics of patients (187 male and 148 female) with type 2 diabetes are shown in Table 1. LJM of hand was present in 80 patients, and these patients had significantly older age, longer duration of diabetes, worse renal function, and higher proportion of diabetic neuropathy, retinopathy and nephropathy. Lymphocyte was significantly lower in patients with LJM of hand ($2,093 \pm 931$ vs. $1,865 \pm 765$, $p = 0.049$) whereas neutrophil was not

different between groups ($3,665 \pm 1,605$ vs. $3,624 \pm 1,853$, $p = 0.848$), then NLR in patients with LJM of hand was higher than that in patients without LJM of hand (2.54 ± 1.46 vs. 2.11 ± 1.04 , $p = 0.004$) (Table 1). We performed the comparison analyses between NLR and several variables including the presence of neuropathy, retinopathy and nephropathy. NLR was significantly higher in the groups of hypertension, neuropathy, retinopathy and nephropathy (Table 2). In univariate logistic regression analyses, LJM of hand was correlated with age, male sex, duration of diabetes, BMI, hypertension, dyslipidemia, microangiopathy and NLR. Multivariate logistic regression analysis revealed that LJM of hand was positively correlated with NLR (OR, 1.31; 95% CI, 1.03–1.69) after adjustment for age, sex, duration of diabetes, BMI, HbA1c, hypertension, and dyslipidemia (Table 3).

Table 1 Clinical characteristics of patients

	LJM (–) ($n = 255$)	LJM (+) ($n = 80$)	<i>P</i>
Age (years)	65.7 ± 12.7	72.8 ± 11.1	<0.001
Male (%)	39.6	58.7	0.003
BMI (kg/m^2)	25.0 ± 4.9	23.7 ± 4.9	0.046
Hemoglobin A1c (%)	7.4 ± 1.1	7.7 ± 1.2	0.074
Duration of type 2 diabetes (year)	14.8 ± 8.9	20.6 ± 10.5	<0.001
eGFR ($\text{mL}/\text{min}/1.73 \text{ m}^2$)	68.3 ± 23.4	59.7 ± 20.4	0.005
Creatinine ($\mu\text{mol}/\text{L}$)	77.4 ± 31.5	72.3 ± 25.6	0.154
Systolic blood pressure (mmHg)	132.5 ± 18.2	132.8 ± 19.4	0.850
Dyastolic blood pressure (mmHg)	74.8 ± 52.9	67.6 ± 12.9	0.241
Total cholesterol (mmol/L)	4.55 ± 0.83	4.56 ± 0.88	0.980
Triglyceride (mmol/L)	1.71 ± 1.07	1.78 ± 1.35	0.605
WBC ($/\text{mm}^3$)	6.69 ± 1.88	6.8 ± 2.16	0.656
Neutrophil ($/\text{mm}^3$)	$3,665 \pm 1,605$	$3,624 \pm 1,853$	0.848
Lymphocyte ($/\text{mm}^3$)	$2,093 \pm 931$	$1,865 \pm 765$	0.049
NLR	2.11 ± 1.04	2.54 ± 1.46	0.004
Hypertension (%)	62.7	82.5	0.001
Dyslipidemia (%)	59.2	73.7	0.019
Neuropathy (%)	31.3	65.0	<0.001
Retinopathy (%)	25.5	51.3	<0.001
Nephropathy (%)	42.7	67.5	<0.001

Continuous variables are presented as the mean value $\pm$ 1 SD. Categorical variables are presented as a number (percentage). LJM, limited joint mobility; BMI, body mass index; eGFR, estimated glomerular filtration rate; WBC, white blood cell; NLR, neutrophil-lymphocyte ratio.

Table 2 NLR in several clinical variables

	NLR	<i>p</i>
Sex (male/female)	2.01 ± 0.78/1.99 ± 0.75	0.863
Hypertension (–/+)	1.85 ± 0.71/2.07 ± 0.84	0.015
Dyslipidemia (–/+)	1.97 ± 0.71/2.02 ± 0.80	0.597
Neuropathy (–/+)	1.92 ± 0.76/2.13 ± 0.77	0.019
Retinopathy (–/+)	1.94 ± 0.68/2.14 ± 0.91	0.037
Nephropathy (–/+)	1.87 ± 0.69/2.15 ± 0.82	0.001

Continuous variables are presented as the mean value ± 1 SD. NLR, neutrophil-lymphocyte ratio.

Discussion

In this study, we evaluated the relationships between LJM of hand and NLR in patients with type 2 diabetes and multivariate logistic regression analysis indicated that LJM of hand was correlated with NLR after adjusted for several factors. To the best of our knowledge, this is the first report investigate the relationship between LJM of hand and NLR. LJM of hand is one of the complications of ‘Diabetic hand’, which is tended to be overlooked [6]. Relationship between diabetic hand especially LJM of hand, and micro and macro vascular complications were previously reported [1–6, 8, 9]. NLR, including components both neutrophils and lymphocytes, has been recently described as a simple and novel inflammatory marker in cancer and cardiovascular disea-

ses [16, 18, 27, 28]. Elevated NLR levels were correlated with an increased risk of developing hypertension [29]. NLR was related to the prevalence and incidence of type 2 diabetes and insulin resistance [19]. Furthermore, NLR is reported to be associated with microvascular complications [20, 21, 30, 31]. Previous report indicated that increased NLR was significantly associated with diabetic nephropathy, and high NLR values might be a reliable predictive marker of early-stage diabetic nephropathy [21]. Other study reported that patients with diabetic retinopathy had increased NLR values compared with diabetic patients who did not have retinopathy [30]. NLR was related to the prevalence and severity of coronary arterial disease [32]. In this study, multivariate logistic regression analysis indicated that LJM of hand was correlated with NLR after adjusted for several factors. In recent year, positive association between NLR and diabetic peripheral neuropathy (DPN) is reported [33, 34]. The relation between LJM of hand and NLR might be similar to some extent with the microvascular complications including DPN which were well-known comorbidities of LJM of hand. The precise pathogenesis of LJM of hand is incompletely understood although several studies have revealed the relationship between chronic inflammation and diabetes and its complications [12, 35, 36]. NLR including two different immune system; neutrophils which are related to ongoing inflammation [14] and lymphocytes which reflected the immune regulatory pathway [15]. NLR represents the balance between neu-

Table 3 Univariate and multivariate-adjusted ORs (95% CI) for risk factors associated with LJM of hand

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	<i>p</i>	OR (95%CI)	<i>p</i>
Age	1.05 (1.03–1.08)	<0.001	1.04 (1.01–1.07)	0.009
Male	2.39 (1.42–4.06)	0.001	2.04 (1.10–3.79)	0.023
Duration of diabetes	1.06 (1.03–1.09)	<0.001	1.04 (1.01–1.07)	0.023
BMI	0.94 (0.89–0.99)	0.042	0.98 (0.91–1.05)	0.633
Hemoglobin A1c	1.21 (0.98–1.49)	0.080	1.30 (1.00–1.70)	0.051
Creatinine	0.99 (0.59–1.43)	0.988	—	—
Smoking	0.69 (0.32–1.59)	0.374	—	—
Hypertension	2.79 (1.53–5.44)	0.001	1.63 (0.74–3.81)	0.226
Dyslipidemia	1.94 (1.12–3.45)	0.017	1.43 (0.71–2.99)	0.319
NLR	1.33 (1.09–1.64)	0.006	1.31 (1.03–1.69)	0.027

Data are expressed as mean ± SD. LJM, limited joint mobility; BMI, body mass index; eGFR, estimated glomerular filtration rate; NLR, neutrophil-lymphocyte ratio.

trophils and lymphocyte, and is thought to be an indicator of systemic inflammation [17]. This might partially explain the reason why NLR correlated LJM of hand. Inflammation has an important role in the development of vascular complications in diabetic patients, therefore diabetes and its complications had been demonstrated as an inflammatory disease [11, 12]. Formation of advanced glycosylation end-products (AGEs), hyperglycemia and oxidative stress were also thought to be related with the development of LJM of hand [37-39]. In this study, we identified that NLR correlated with LJM of hand in patients with type 2 diabetes. LJM of hand, which is associated with diabetic micro- [1-4, 7] and macro-complications [8, 9, 40], is relatively easy to notify; however, clinicians often overlook this complication of diabetes in clinical situations [6]. NLR, which calculated simply and easily in routine clinical practice, could be used as a marker of diabetic complications including LJM of hand.

This study has several limitations. First, the cross-sectional design only permits inference of the causal relationships between NLR and LJM of hand. Second, we did not investigate other diabetic hand such as Dupuytren's contracture or carpal tunnel syndrome. However, it is likely that these hand syndromes are also associated with NLR because the same pathologies such as microvascular disease or abnormal collagen deposition are hypothesized [38]. Third, we did not evaluate NLR with other inflammatory mediators such as high sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-alpha and interleukin 6, so we could not detect whether NLR was a better inflammatory marker in this research although previous report indicated that NLR correlated with hs-CRP and had a specific role to detect DPN rather than other inflammation factors [33]. Finally, the patients in this study were all Japanese, and it is uncertain if these findings are general.

In summary, we investigated the positive relationship between NLR and LJM of hand in patients with type 2 diabetes. Further study is needed to evaluate the application for NLR to predict LJM of hand in patients with type 2 diabetes.

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Conflict of Interest

Michiaki Fukui has received grants, honoraria and research supports from AstraZeneca plc., Astellas Pharma Inc., Nippon Boehringer Ingelheim Co., Ltd., Daiichi Sankyo Co., Ltd., Eli Lilly Japan K.K., Kyowa Hakko Kirin Company Ltd., Kissei Pharmaceutical Co., Ltd., MSD K.K., Mitsubishi Tanabe Pharma Corporation, Novo Nordisk Pharma Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., Sanofi K.K., Ono Pharmaceutical Co., Ltd., and Takeda Pharmaceutical Co., Ltd. The sponsors were not involved in the study design; in the collection, analysis, interpretation of data; in the writing of this manuscript; or in the decision to submit the article for publication. The authors, their immediate families, and any research foundations with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article. The authors declare that although they are affiliated with a department that is supported financially by pharmaceutical company, the authors received no current funding for this study and this does not alter their adherence to all the journal policies on sharing data and materials. The other authors have nothing to disclose.

Contributors

YM contributed to the conception and design, wrote the manuscript, and researched and analyzed data. MI contributed to acquisition of data, critical revision of the manuscript, and analysis and interpretation of data, and approved the final version of the manuscript. YH contributed to critical revision of the manuscript, and to analysis and interpretation of data. NN and YK contributed to revision of the manuscript. MI contributed to acquisition of data and reviewed the manuscript. MF contributed to critical revision of the manuscript.

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