Diabetic Nephropathy- Can Neutrophil Lymphocyte Ratio Predict the Presence of Albuminuria?

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ABSTRACT

BACKGROUND
Diabetic nephropathy (DN) is the leading cause of end stage renal disease requiring renal replacement therapy. Albuminuria occurs early in DN and there is increasing evidence to suggest that the pathogenesis of DN is related to the degree of systemic inflammation. NLR being an easily available dynamic parameter, is a novel marker of systemic inflammation and may have a role in diagnosis of albuminuria in DN.

METHODS
This is a cross-sectional observational study conducted among 150 patients diagnosed with type 2 diabetes mellitus (T2DM). NLR was calculated from differential leucocyte count and albuminuria was calculated using urine albumin creatinine ratio (UACR).

RESULTS
Out of the total of 150 patients, 63 patients had albuminuria and 87 did not have albuminuria. Mean neutrophil-lymphocyte ratio in patients with diabetic nephropathy was 2.76±0.81 as compared to those without nephropathy (1.94±0.74), which was statistically significant.

CONCLUSIONS
There was a statistically significant correlation between NLR and presence of DN which suggests that NLR could be used as a diagnostic tool for albuminuria in patients with T2DM patients not suffering from any infective or inflammatory disorders.

KEYWORDS
Diabetic Nephropathy, Neutrophil-Lymphocyte Ratio, Albuminuria

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DOI: 10.18410/jebmh/2019/655

Financial or Other Competing Interests: None.

How to Cite This Article:
Phaneesh Bharadwaj BS, Pujitha SN. Diabetic nephropathy- can neutrophil lymphocyte ratio predict the presence of albuminuria? J. Evid. Based Med. Healthc. 2019; 6(50), 3130-3133. DOI: 10.18410/jebmh/2019/655

Submission 22-11-2019,
Peer Review 24-11-2019,
Acceptance 01-12-2019,
Published 12-12-2019.

BACKGROUND

India is the diabetic capital of the world and diabetes is known to cause variable micro and macro-vascular complications like diabetic nephropathy (DN), retinopathy (DR), neuropathy (DN), stroke, coronary artery disease, and peripheral vascular disease.[1] Diabetic nephropathy is the leading cause for end stage renal disease (ESRD)[2] requiring renal replacement therapy. Albuminuria occurs early in diabetic nephropathy (DN) and predicts future worsening of renal function. There is increasing evidence to suggest that the pathogenesis of DN is related to the degree of systemic inflammation.[3] Various markers of inflammation have been found to be associated with DN, such as interleukin-1 (IL1), IL6, IL8, transforming growth factor beta 1, tumor necrosis factor-alpha (TNF-a), and cytokines.[4,5] However, measurement of these parameters cannot be readily done. A simpler parameter like Neutrophil lymphocyte ratio (NLR) has been shown to be an inexpensive and accurate marker of systemic inflammation.[6] Complete blood count (CBC) is a common investigation done even in a peripheral primary healthcare centre where accurate assessment of DN may be difficult and hence NLR if associated with albuminuria will help in early detection of DN.

METHODS

A total of 150 patients diagnosed with type 2 diabetes mellitus who presented for management of diabetes without any acute illness after considering inclusion and exclusion criteria were included in the study. Data was obtained with a detailed history, clinical examination and laboratory studies. As most of the patients were in the elderly age group, those who had hypertension were on calcium channel blockers and beta blockers. Qualitative data and quantitative data obtained were then analysed for any significant correlations with special importance to NLR and urine albumin creatinine ratio (UACR). The study protocol was approved by the Institutional Ethics Committee, and the written informed consent was taken from all participants before their inclusion in the study.

Relevant blood investigations such as complete blood picture, Blood urea, serum creatinine, urine dipstick and microscopy, fasting blood sugar (FBS) &postprandial blood sugar (PPBS), glycated haemoglobin (HbA1c) and ultrasonography of the abdomen with kidney size measurement were done. Fundus examination was done to assess diabetic retinopathy. Albuminuria was tested using random urine albumin creatinine ratio (UACR). UACR of 30-300 mg/g of creatinine was considered as microalbuminuria.[7-9]

Patient were divided into 2 groups based on presence or absence of microalbuminuria. NLR, micro and macrovascular complications were compared between the two groups. NLR was calculated using differential leucocyte count.

Place of Study

This study was done in a tertiary care centre R. L. Jalappa Hospital, Tamaka, Kolar, Karnataka under Sri Devaraj Urs Academy of Higher Education and Research (SDUAHER)

Study Period

Data was collected from all patients with the diagnosis of type 2 diabetes mellitus fulfilling inclusion and exclusion criteria for 1 and half years between time periods of 1st November 2017 to 30th April of 2019.

Study Design

Cross sectional observational study.

Inclusion Criteria

1. Patients diagnosed with type 2 diabetes mellitus

Exclusion Criteria

1. Patients known to be suffering from or having symptoms/signs of any systemic inflammatory disorders- Infectious diseases/connective tissue disorders/malignancy.
2. Pregnancy
3. Renal/ureteric/bladder stones
4. History of smoking or chronic steroid use
5. Use of drugs inhibiting renin angiotensin aldosterone pathway
6. Uncontrolled hypertension (supine arm blood pressure >140/90 mmHg)

RESULTS

In our study total of 150 patients of diagnosed type 2 diabetes mellitus patient's age and gender matched were screened for diabetic nephropathy. Out of these 150 patients 67 patients had diabetic nephropathy and 83 patients did not have microalbuminuria. Various variables such as NLR, diabetic retinopathy, glycated haemoglobin were compared in both the groups. Mean age groups of patients in normal and diabetic nephropathy were 56.4± 10.8 years and 58.3± 12.7 years respectively with P value of 0.32(not significant). Also, there was a statistically significant difference between duration of diabetes and diabetic nephropathy (P value-0.0461).

Parameter	With DN (n=67)	Without DN (n=83)	p
Mean age (in years)	58.3±12.7	56.4±10.8	0.3228
Duration of diabetes	6±3.84	5±2.16	0.0461
Gender- Female Male	32 35	38 45	0.8653
FBS (mg/dl)	157± 24.8	146±19.4	0.0027
PPBS (mg/dl)	232±34.7	219±37.4	0.034
HbA1c (g%)	8.78±1.6	7.96±1.4	0.001
Blood urea	27.5±16.3	26.3±15.2	0.64
Serum creatinine	1.1±0.8	1.0±0.8	0.4478
Controlled HTN	26(38.8%)	31(37.34%)	0.8673
Obesity	24(35.8%)	36(43.37%)	0.4032

Table 1. Comparison of Baseline Parameters in Patients with and without Diabetic Nephropathy

There was no statistically significant gender differentiation, hypertension and obesity between both the groups. Several parameters like FBS, PPBS, HbA1c and renal function tests were compared between both the groups as shown in Table 1. Statistically significant (p value<0.05), FBS= Fasting Blood Glucose, PPBS= Postprandial Blood Glucose, HbA1c= Glycated Haemoglobin percentage.

The difference in neutrophil-lymphocyte ratio between the two groups (diabetic nephropathy vs no nephropathy) was statistically significant (p value <0.001) in group with as shown in Table 2. Out of the total 150 patients 84(56%) patients had diabetic retinopathy and out of which 51(60%) patients had nephropathy as well which implies that 51(34%) of the patients had both diabetic retinopathy and nephropathy (Table 3). There was also statistically significant (P value <0.001) difference in NLR ratio in patients with DR and DN (Table 4).

Parameter	With DN (n=67)	Without DN (n=83)	p
NLR	2.76±0.81	1.94±0.74	0.0001

Table 2. Comparison of Neutrophil-Lymphocyte Ratio in Patients with and without Diabetic Nephropathy

Statistically significant (p value<0.05), NLR= neutrophil-lymphocyte ratio.

DR	DN		Chi Square	p
	Yes	No		
Yes (84)	51(60%)	33 (40%)	10.8	0.005
No (66)	24 (36.3%)	42 (63.7%)		

Table 3. Relationship between Diabetic Nephropathy and Retinopathy

Statistically significant (p value <0.05), NLR= neutrophil-lymphocyte ratio.

Parameter	With DN & DR (n=51)	Without DN & DR (n=42)	p
NLR	2.87±1.2	2.13±0.8	0.0009

Table 4. Correlation of NLR in Group with and without Both Nephropathy, Retinopathy

Statistically significant (p value<0.05), NLR= neutrophil-lymphocyte ratio, DN-diabetic retinopathy, DR-diabetic retinopathy.

DISCUSSION

This study was done with a main purpose to study the utility of a simple and easily available marker of inflammation such as NLR in the evaluation of DN. The role of inflammation in the pathogenesis of diabetic nephropathy is gaining importance with recent studies showing a strong association of systemic inflammation and diabetic nephropathy. Various markers of inflammation such as interleukin-1 (IL1), IL6, IL8, transforming growth factor beta 1, tumour necrosis factor-alpha (TNF-a), and cytokines have been found to be associated with DN.(4,5) As these are not readily available and due to cost factors, NLR measurement appears to be a more practical and relevant marker of diabetic nephropathy. Over the last few decades multiple studies have been done to show the relation between inflammatory markers and endothelial dysfunction with diabetes and its complications.[10-15] Studies have been conducted implicating neutrophilia and relative lymphocytopenia as independent markers of diabetic nephropathy and other diabetes related complications.[4,5,16,14,15,17] NLR being a dynamic parameter, is a novel marker of systemic inflammation and has a high prognostic value in coming to a diagnosis or indicating severity of a disease.[4,5,18] Since T2DM has a significant correlation with systemic inflammation, NLR could be used to predict the occurrence or severity of complications.

In our study there was a statistically significant (p value 0.0001) increase in neutrophil-lymphocyte ratio in patients with diabetic nephropathy (2.76±0.81) as compared to those without nephropathy (1.94±0.74). There was also a significant (0.0009) association of NLR with those patients who had both diabetic nephropathy and retinopathy (2.87±1.2) compared to those who did not have both (2.13±0.8).

A study done by Ulu et al.[19] demonstrated that NLR had a significant association with prognosis and severity of diabetic retinopathy as well as sensori neural hearing loss in patients with diabetes mellitus. In another study by Afsar[20] it was shown that NLR could be associated with DN and an indicator of ESRD. Similar to the results in our study, Huang et al.[21] found that NLR values were significantly higher in diabetic patients with evidence of nephropathy (2.48 ± 0.59) than in diabetic patients without nephropathy (2.20 ± 0.62). In reference to other parameters used, FBS and HbA1c had significant association with DN than PPBS. It was also seen that there was no significant correlation between blood urea or serum creatinine with presence of albuminuria.

CONCLUSIONS

There was a statistically significant correlation between NLR and presence of DN which suggests that NLR could be used as a diagnostic tool for albuminuria in patients with T2DM patients not suffering from any infective or inflammatory disorders.

Limitations

The first limitation of this study was that a random UACR was performed in place of first morning UACR due to practical limitations. Secondly, dyslipidaemia and its potential contribution to albuminuria was not assessed in the study patients as the intention was to use tests which were readily available in an Indian rural healthcare setting.

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