Neutrophil-to-lymphocyte ratio in diabetes mellitus patients with and without diabetic foot ulcer

Cüneyt Kahraman[1], Gündüz Yümün[2], Nilüfer Kuzeyli Kahraman[1], Nazli Dizen Namdar[3], Süleyman Cosgun[1]

[1]M.D. Dumlupinar University Evliya Çelebi Research and Education Hospital, Department of Internal Medicine

[2]M.D. Dumlupinar University Evliya Çelebi Research and Education Hospital, Department of Cardiovascular Surgery

[3]M.D. Dumlupinar University Evliya Çelebi Research and Education Hospital, Department of Dermatology

Abstract

Background: Diabetes mellitus (DM), with the cost of treatment and complications causes the increasing economic burden. Inflammation in the pathogenesis of type 2 DM and developing complications are considered to have a role. Macrovascular complications of diabetes, diabetic foot ulcers and amputations consequently reduce quality of life is seriously. Atherosclerosis and related complications is considered as an inflammatory process. To show the severity and course of this inflammatory process, the studies including many markers are available. Recently, it is reported as a cheap and accessible marker, neutrophil/lymphocyte ratio (NLR) is a good indicator of the inflammatory condition. The aim of this study to investigate the relationship between the presence of the diabetic foot and neutrophil / lymphocyte ratio. **Methods:** It has been noted retrospectively the charts of the data of internal medicine clinic patients with diabetes. Patients' age, sex, duration of diabetes, blood count and biochemical parameters were recorded. The data of patients with and without diabetic foot ulcers were assessed using SPSS 19.0. **Results:** Statistically significant differences were also observed according to HbA1c (P = 0.006), serum urea (P = 0.042), CRP (P < 0.001), neutrophil percent (P < 0.001), lymphocyte percent (P < 0.001), NLR (P = 0.001), among the 2 groups. A correlation was determined between NLR and age, serum urea, creatinine, white blood cell (WBC), neutrophil percent, lymphocyte percent, total cholesterol, HDL-cholesterol. **Conclusion:** The presence of diabetic foot ulcers alone may also represent a systemic inflammatory response. NLR can be a cheap and accessible marker for presence of this inflammatory process via using the response rates and follow-up of patients.

Key Words: Diabetic foot ulcer**,** macrovascular complications, neutrophil/lymphocyte ratio.

Correspondence Address: Cüneyt Kahraman. Dumlupinar University School of Medicine. Assistant professor of Internal Medicine, M.D. Dept. of Internal Medicine. Kutahya, Turkey
Phone: +90 505 3930536 E mail: kahramandoktor@gmail.com

Introduction

DM type-2 because of diabetes-related complications lead to significant many socio-economic problems. These are microvascular [diabetic nephropathy, neuropathy and retinopathy] and macrovascular complications [atherosclerosis, ischemic heart disease, stroke and peripheral vascular disease that often results with amputation] (1). One of chronic complications is diabetic foot that is a multifactorial problem with neuropathy and peripheral vascular disease addition to the infection caused by the extremities. Diabetic foot disease, diabetic population has become the most important cause of hospitalization and accounted length of stay 20-25%. 50% of nontraumatic amputations are due to diabetic foot (2). Diabetic foot can led to losses of tissues and organs, for reasons such as infection it is a long and distressing process for patients, relatives of patients and a privileged entity in society which is a heavy economic burden (3, 4, 5).

Many epidemiological studies have highlighted that chronic low grade inflammation is associated with diabetes mellitus (6), hypertension (7), metabolic syndrome (8, 9), obesity (10), smoking (11), and other lifestyle habits (12). Systemic inflammation can be measured by using a variety of biochemical and haematological markers. Although novel disease specific biomarkers have been identified, most of which are time consuming and expensive. Observational studies have thoroughly investigated the role of C-reactive protein and total leukocyte count in different chronic conditions (13, 14, 15, 16). Low grade inflammation measured by White Blood Cell (WBC) count has also been linked to the traditional risk factors of chronic diseases i.e. smoking, obesity, hypertension and elevated levels of triglycerides (16, 17). Recent evidence indicated that the ratio of sub types of blood cells have a significant prognostic value for cardiovascular disease. Neutrophil-to-lymphocyte ratio is a potential marker for inflammation in cardiac and non-cardiac

disorders (18, 19). Neutrophil lymphocyte ratio could be an important measure of systemic inflammation as it is cost effective, readily available and could be calculated easily. Little is known and published about neutrophil lymphocyte ratio and its relationship with prevalent chronic conditions among general population. Therefore, the current study was conducted to investigate the neutrophil lymphocyte ratio as a measure of systemic inflammation and its relationship, if any, with prevalent chronic diseases (20).

In this study, our objective was to examine the relationship with NLR, showing the presence of systemic inflammation in the presence of diabetic foot ulcer.

Materials and Methods

In this study, due to diabetes mellitus internal diseases clinic followed by a total of 62 with and without diabetic foot ulcers (31 diabetics with ulcers, non-ulcer 31) patients were included retrospectively. Patient demographic data including age, gender, disease duration, further laboratory data as a complete blood count (hemoglobin level, platelet count, MPV, neutrophil count, lymphocyte count, NLR, RDW), blood chemistry (urea, creatinine, total cholesterol, HDL, LDL, TG, HbA1c) C-reactive protein (CRP) levels were recorded. The study has not included active infection, leukocytosis, malignancy, steroid use without any reason.

Statistical analysis was conducted using SPSS version 19 (SPSS, Chicago, IL). Normality was assessed using a Shapiro-Wilk test. For normally distributed values, descriptive results are expressed as mean+ SD. The independent-samplest-test and Kruskal-Wallis test were used to examine the differences between groups. For the post hoc analysis among these groups, Bonferroni corrected Mann-Whitney's U test was used. Statistical significance was defined as $P < 0,05$.

Results

A total of 62 patients who comply with the criteria have been included in this study. Diabetic foot ulcer group consisted of 31 patients (12 females, 19 males) with a mean age of 61,1 ± 11 years. Control group consisted of 31 non ulcer (17 females, 14 males) with a mean age of 60,1 ± 9,4 years. There was no statistically significant difference between groups by means of female / male gender ratio (P = 0.346). Demographic parameters of the patients were given in Table 1. Furthermore, there was no statistically significant difference by means of diabetes, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol,

WBC, hematocrit level, platelet count, MPV and RDW. Statistically significant differences were also observed according to HbA1c (P = 0.006), serum urea (P = 0.042), CRP (P < 0.001), neutrophil percent (P < 0.001), lymphocyte percent (P < 0.001), NLR (P = 0.001), among the 2 groups (Table-2).

Pearson correlation analysis revealed that NLR was correlated with age (r =0.261, P = 0.041), serum urea (r = 0.468, P < 0.001), creatinine (r = 0.443, P < 0.001), WBC (r = 0.594, P < 0.001), neutrophil percent (r = 0.765, P<0.001), lymphocyte percent (r = -0.742, P<0.001), total cholesterol (r = -0.391, P = 0.002), HDL-cholesterol (r = -356, P = 0.005).

Table 1. Descriptive Statistics of Population

Variables	Diabetic foot ulcer n = 31	Diabetic control group n = 31	P
Age (years)	61,1 ± 11	60,1 ± 9,4	0.549
Sex (% female)	38,7	54,8	0.346
Duration of diabetes (years)	5.6 ± 4.0	5.4 ± 3.3	0.792

Discussion

Diabetes have severe effects on the vascular system. Large, medium-sized arteries are seen rapid and severe atherosclerosis. The result of advanced vascular disease, lower extremities gangrene in diabetics is seen a hundred times more often than the general population (21). Cause of hospitalization of diabetic, approximately 50% are chronic complicati ons, this case has resulted with the high cost of treatment and an increased loss of manpower. Diabetic foot ulcers which is one of the determining factors of duration and quality of life by diabetic patients, are among the most frequent cause of hospitalization and surgical intervention. In recent years, rather than depending on lipid infiltration of atherosclerosis a passive vascular damage it is emphasized that an active inflammatory occurs as a result of this process (22). Many markers have been proposed indicating of these inflammatory processes

severity. Finally NLR has been suggested as an indicator of subclinical inflammation and proved the relation prognosis between both coronary artery disease and heart failure (23). Recent studies have shown that NLR as microvascular complications of diabetes is related with the presence of nephropathy and it has been correlated as an indicator of end stage renal failure with albuminuria levels (24). DM is not only a metabolic disorder, is now known that several molecules associated with inflammation in the development of diabetes and diabetes-related complications may play an important role (25, 26). Diabetes mellitus has been reported to be associated with acute phase response. In type 2 diabetes, sialic acid, α-1 acid glycoprotein, C-reactive protein (CRP), serum acute phase reactants such as amyloid and mediator cytokine IL-6 has been shown to be increased (27).

Table 2. Laboratory Results of the Two Groups

Variables	Diabetic foot ulcer n = 31	Diabetic control group n = 31	P
Hba1c	8.9 ± 2.2	10.7 ± 2.3	0.006
Total cholesterol (mmol/l)	184.6 ± 43.8	182.7 ± 43.4	0.300
Triglyceride (mmol/l)	199.5 ± 126.2	232.2 ± 153.8	0.266
HDL-cholesterol (mmol/l)	38,8 ± 19,7	45.1 ± 12.3	0.457
LDL-cholesterol (mmol/l)	109.7 ± 36.8	115.9 ± 39.1	0.711
Serum urea (mg/dL)	40.2 ± 16.1	32.7 ± 10.5	0.042
Creatinine	0.99 ± 0.34	0.84 ± 0.24	0.043
CRP	1.5 ± 1.7	0.6 ± 0.4	<0.001
WBC	9.2 ± 2.9	7.3 ± 2.1	0.236
Hematocrit level, g/dL	36.8 ± 6.7	40.8 ± 7.5	0.569
Platelet count (10^3/mm3)	257.4 ± 84.2	243.3 ± 81.7	0.554
MPV (fL)	8.9 ± 1.5	8.9 ± 1.2	0.602
Neutrophil percent (%)	68.4 ± 10.1	52.5 ± 9.6	<0.001
Lymphocyte percent (%)	21.7 ± 8.1	35.9 ± 8.9	<0.001
NLR	4.3 ± 3.9	1.6 ± 0.7	0.001
RDW	14.9 ± 2.6	14.2 ± 2.2	0.304

* CRP, C-reactive protein; WBC, White blood cell; MPV, Mean platelet volume;
NLR, neutrophil/lymphocyte ratio; RDW, Red cell distribution width.

The studies which are done by Çürüksulu and his colleagues, compared the groups with diabetic foot ulcers and non-ulcer groups. They show significantly higher the levels of IL-6 and high sensitive CRP (hs-CRP), erythrocyte sedimentation, leukocyte count and HbA1c levels (28). In our study we used as a marker of inflammation CRP and NLR and it was significantly higher in the group with ulcers. Our data supported the studies data that have done previously conducted for the inflammatory status. However, in our study, HbA1c levels were significantly lower in the group with ulcers. We thought because of this result that the increasing in hospital admissions of patients with diabetic foot ulcers sugar can be regulated.

Conclusion

In this study, patient with diabetic foot ulcers and non-ulcer has been analyzed NLR level as inflammatory marker. Determining NLR in the presence of high levels of diabetic foot ulcers is not a local inflammation alone but also showed that there is a systemic inflammatory response. In patients with diabetic foot other macrovascular complications of diabetes can be seen much more and using NLR has been suggested as a cheap and accessible inflammatory markers for developing and following of macrovascular complication. In this regard, more extensive and more studies with more several patients are needed.

References

1. Wild, S., Roglic, G., Green, A., Sicree, R., and King, H. (2004). Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 27,1047–1053.

2. Levin ME. Foot lesions in patients with diabetes mellitus. End Met Clin North Amer 1996; 25: 447-462.

3. Mark P, Sloven Ki. Foot problems in diabetes. Med Clin North Am. 1998; 82 (4):949-71.

4. Laing P. The development and conıplications of diabetic foot ulcers. Am J Surg. 1998 Aug 176 (Suppl 2A): 11-19

5. Levin ME. Foot lesions in patients with diabetes mellitus. End Metab Clin North Am.1996; 5 (2): 448-54.

6. Pitsavos C, Tampourlou M, Panagiotakos DB, Skoumas Y, Chrysohoou C, Nomikos T, et al: Association Between Low-Grade Systemic Inflammation and Type 2 Diabetes Mellitus Among Men and Women from the ATTICA Study. Rev Diabet Stud 2007, 4:98-104.

7. Nakanishi N, Sato M, Shirai K, Suzuki K, Tatara K: White blood cell count as a risk factor for hypertension; a study of Japanese male office workers. J Hypertens 2002, 20:851-857.

8. Bell DS, O'Keefe JH: White cell count, mortality, and metabolic syndrome in the Baltimore longitudinal study of aging. J Am Coll Cardiol 2007, 50:1810-1811.

9. Marsland AL, McCaffery JM, Muldoon MF, Manuck SB: Systemic inflammation and the metabolic syndrome among middle-aged community volunteers. Metabolism 2010, 59:1801-1808.

10. Brooks GC, Blaha MJ, Blumenthal RS: Relation of C-reactive protein to abdominal adiposity. Am J Cardiol 2010, 106:56-61.

11. Yasue H, Hirai N, Mizuno Y, Harada E, Itoh T, Yoshimura M, et al: Low-grade inflammation, thrombogenicity, and atherogenic lipid profile in cigarette smokers. Circ J 2006, 70:8-13.

12. Pirkola J, Vaarasmaki M, Ala-Korpela M, Bloigu A, Canoy D, Hartikainen AL, et al: Low-grade, systemic inflammation in adolescents: association with early-life factors, gender, and lifestyle. Am J Epidemiol 2010, 171:72-82.

13. Lee S, Choe JW, Kim HK, Sung J: High-Sensitivity C-Reactive Protein and Cancer. J Epidemiol 2011.

14. Saito K, Kihara K: Role of C-reactive protein as a biomarker for renal cell carcinoma. Expert Rev Anticancer Ther 2010, 10:1979-1989.

15. Bovill EG, Bild DE, Heiss G, Kuller LH, Lee MH, Rock R, et al: White blood cell counts in persons aged 65 years or more from the Cardiovascular Health Study. Correlations with baseline clinical and demographic characteristics. Am J Epidemiol 1996, 143:1107-1115.

16. Freedman DS, Joesoef MR, Barboriak JJ, Stallone DD, Byers T: Correlates of leukocyte counts in men. Ann Epidemiol 1996, 6:74-82.

17. Facchini F, Hollenbeck CB, Chen YN, Chen YD, Reaven GM: Demonstration of a relationship between white blood cell count, insulin resistance, and several risk factors for coronary heart disease in wome. J Intern Med 1992, 232:267-272.

18. Tamhane UU, Aneja S, Montgomery D, Rogers EK, Eagle KA, Gurm HS: Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. Am J Cardiol 2008, 102(6):653–7.

19. Walsh SR, Cook EJ, Goulder F, Justin TA, Keeling NJ: Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. J Surg Oncol 2005, 91(3):181–4.

20. Imtiaz, Fauzia, et al. "Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population." Int Arch Med 5.1 (2012): 2.

21. Aydanur K. Endokrin sistem.In: Temel Patoloji. Edited by Çevikbaş U. İstanbul, Nobel, 2000, pp: 637-666.

22. Masoudkabir F, Karbalai S, Vasheqhani-Farahani A et al. The association of liver transaminase activity with presence and severity of premature coronary artery disease. Angiology 2011;62(8):614-9.

23. Uthamalingam S, Patvardhan EA., Subramanian S et al. Utility of the Neutrophil to Lymphocyte Ratio in Predicting Long-Term Outcomes in Acute Decompensated Heart Failure. Am J Cardiol 2011;107(3):433-8.

24. Afsar B. The Relationship Between Neutrophil Lymphocyte Ratio With Urinary Protein and Albumin Excretion in Newly Diagnosed Patients With Type 2 Diabetes. Am J Med Sci. 2013 Feb 25.

25. Pickup, J.and Crook, M. (1998)Is type II diabetes mellitus a disease of the innate immune system. Diabetologia41, 1241–1248.

26. Navarro, J.F. and Mora, C.(2005) Role of inflammation on diabetic complications. Nephrol. Dial. Transplant.20, 2601–2604.

27. JC Pickup, MB Mattock, GD Chusney, D Burt, NIDDM as a disease of the İnnate immune system: Association of acute-phase reactants and IL-6 with metabolic syndrome X, Diabetologia 1997; 40:1286-1292

28. Çürüksulu, Hayrettin, et al. "Diyabetik ayak komplikasyonu bulunan ve bulunmayan DM'li hastalarda serum interlökin-6 ve HS-CRP düzeyleri." Haseki Tıp Bülteni 43 (2005): 121-125.