ORIGINAL RESEARCH

A study of Neutrophil Lymphocyte Ratio as amarker for Endothelial Dysfunction and Insulin Resistance among individuals with Type 2 Diabetes

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ABSTRACT
Aim and objectives: The aim of the study was to assess the Neutrophil Lymphocyte Ratio as a markerof Endothelial Dysfunction and Insulin Resistance in patients with Type 2 Diabetes. **Materials and method:** The present study was a hospital based cross-sectional study carried out in the department of clinical medicine.Neutrophil and lymphocyte ratio (N/L ratio) was calculated by doing complete blood count. Then the ratio of the absolute neutrophil count to absolute lymphocyte count will be calculated.Insulin resistance was assessed by HOMA-IR. Endothelial dysfunction was detected non-invasively by ultrasonographic analysis of brachial artery-flow mediated vasodilatation (FMD). **Results:** There were 58.0% males and 42.0% females mean age of 49.88±10.91 (range = 32.00-78.00) years. There was a significantly positive correlation of NL ratio with Fasting blood sugar, HbA1C%, Ultrasound guided Flow mediated vasodilatation (FMD), Serum Insulin and HOMA-IR2. **Conclusion:** NLR deterioration is associated with glycaemic disorder, which increases the importance of haemogram in diabetic patients. Improvement of NLR after glycaemic regulation has suggested that this parameter may be more useful in demonstrating glycaemic regulation rather than complications.
Keywords: HOMA-IR, HbA1C%, Ultrasound guided Flow mediated vasodilatation, Neutrophil and lymphocyte ratio

INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia.(1) Several distinct types of DM are caused by a complex interaction of genetics and environmental factors.[1] It is characterized by high blood glucose levels resulting from defects in insulin production, insulin action, or both.[2,3]

Diabetes mellitus (DM) is categorized into to broad categories DM Type 1 and DM type 2.Type 2 diabetes mellitus is the predominant form of diabetes worldwide. The incidence of diabetes is increasing day by day. The epidemic of diabetes is under way in both developing and developed countries.Type 2 Diabetes Mellitus (T2DM) is characterized by insulin resistance and is associated with obesity and cardiovascular diseases.[4]

Several studies that explored the relationship between systemic inflammation and cardiovascular diseases[5] indicated that chronic inflammation promotes the acceleration of diabetic microangiopathy in addition to the development of macroangiopathy in diabetic patients.[6,7]

Insulin resistance (IR) is a reduction in reaction or sensitivity to insulin and is considered to be the common cause of impaired glucose tolerance, diabetes, obesity, dyslipidemia, and hypertensive diseases. Type 2 diabetes mellitus (DM) has many microvascular and macrovascular complications.[8]The neutrophil-tolymphocyte (N/L) ratio was defined as a

biomarker of inflammation.[9]Increased NLR is associated with severe, extensive and complex CAD.[10,11]

HbA1c is a widely available test which is usually advised by most clinicians to measures the long term glycemic control in diabetic patients over the period of previous 2-3 months. HbA1c also tells about the severity of hyperglycemia and considered to be a biomarker of risk factors for diabetes related micro and macro-vascular complications.[12]

NLR is an important marker of chronic inflammation which exhibits a balance between two interdependent components of the immune system. Neutrophils are the active inflammatory mediator that forms the first line of defense and the high neutrophil count is a marker of the ongoing destructive nonspecific inflammatory process. whereas lymphocytes are the regulatory and protective component of inflammation and low lymphocyte count value indicates relatively inadequate immune regulation.[13,14]

Stimuli such as hyperglycemia and oxidative stress increase the expression of Intracellular Adhesion Molecule 1 (ICAM-1), proinflammatory cytokines, and chemokines.[15]The overexpression of ICAM-1 results in the gathering of inflammatory cells.[16]

The present study was done to assess the Neutrophil Lymphocyte Ratio as a Marker of Endothelial Dysfunction and Insulin Resistance in Patients with Type 2 Diabetes.

MATERIALS AND METHOD

The present hospital based prospective study was carried out in the Department of Clinical Medicine. A total of 50 Patients were taken with Type 2 Diabetes mellitus.After the approval of ethics committee, this study was planned to conduct on different age group patients with diabetes mellitus type 2 disease in out-patient and in-patient department.

STUDY POPULATION

The study included all patients with type 2 diabetes mellitus age >30 years. The study excluded patients with history of any active disease in last 4 weeks, Patients with any underlying hematological disorder and any history of drug intake and alcohol use.

STUDY PROTOCOL

Patients presenting in department of General Medicine with Diabetes mellitus type 2 will be evaluated and thorough history will be taken regarding name, age, sex occupation, residential address, chief complaints, history of presenting illness, history of medical treatment for diabetes and history of previous treatment.

General and systemic examination was done to complete the systemic examination including cardiovascular, central nervous system and abdominal examination. Any abnormality will be recorded. Local examination included Acanthosis nigricans, skin tags.

Neutrophil and lymphocyte ratio(N/L ratio) was calculated by doing complete blood count. Then the ratio of the absolute neutrophil count to absolute lymphocyte count will be calculated.

Insulin resistance was done by HOMA-IR which is calculated by using the followingformula: fasting plasma glucose (mmol/L) multipliedby fasting serum insulin (mIU/L) divided by 22.5.A HOMA-IR value of > 2.0 was indicative of IR. Endothelial dysfunction was detected non-invasively by ultrasonographic analysis of brachial artery-flow mediated vasodilatation (FMD).

STATISTICAL ANALYSIS

SPSS version 25.0 analyzed the Excel data when it was loaded. Quantitative (numerical variables) data was given as mean and standard deviation, whereas qualitative (categorical variables) data was provided as frequency and percentage.The student t-test was used to compare the two groups' mean values, while the chi-square test analyzed their frequency differences. If p-value was less than 0.05, it was statistically significant.

RESULTS

Table 1 showing the basic information

		Frequency	Percent
Age (in years)	30-45 years	18	36.0%
	46-60 years	24	48.0%
	> 60 years	8	16.0%
	Mean±SD	49.88±10.91(32-78)	
Gender	Male	29	58.0%
	Female	21	42.0%

The study population consisted of 18 (36.0%) subjects from 30-45 years, 24 (48.0%) subjects from 46-60 years and 8 (16.0%) subjects from > 60 years age group. The mean age of the study population was 49.88±10.91 (range = 32.00-78.00) years.There were 29 (58.0%) males and 21 (42.0%) females among study population.

Table 2 showing Hemoglobin, TLC, FBS (mg/dl), HbA1c (%), Absolute Lymphocyte (%), Absolute Neutrophil (%) and NL ratio

	Mean±SD (Minimum-Maximum)
Hb	11.94±1.79 (8-16)
TLC	7422.00±1926.54 (4500.00-11500.00)
FBS (mg/dl)	141.08±24.26 (98.00-201.00)
HbA1c (%)	8.57±1.58 (6.60-13.00)
Absolute Lymphocyte (%)	35.60±5.39 (22.00-51.00)
Absolute Neutrophil (%)	62.08±16.18 (45.00-93.00)
NL ratio	0.88±3.40 (1.81-0.63)

The mean Hb levels were 11.94±1.79 (range = 8.00-16.00). The mean TLC value was 7422.00±1926.54 (range = 4500.00-11500.00). The mean FBS (mg/dl) levels were 141.08±24.26 (range = 98.00-201.00). The mean HbA1c (%) was 8.57±1.58 (range = 6.60-13.00). The mean Absolute Lymphocyte (%) was 35.60±5.39 (22.00-51.00). Absolute Neutrophil (%) was 62.08±16.18 (45.00-93.00). The mean NL ratio was 1.81±0.63.

Table 3 showing the correlation of NL ratio with Fasting blood sugar, HbA1C%, Flow mediated vasodilatation, serum insulin levels and HOMA-IR2 levels

		NL ratio
Fasting blood sugar	Pearson Correlation	0.573
	p-value	0.008*
HbA1C%	Pearson Correlation	0.515
	p-value	0.010*
Ultrasound guided Flow mediated vasodilatation (FMD)	Pearson Correlation	0.608
	p-value	< 0.001*
Serum Insulin	Pearson Correlation	0.511
	p-value	< 0.001*
HOMA-IR2	Pearson Correlation	0.546
	p-value	< 0.001*

There was a significantly positive correlation of NL ratio with Fasting blood sugar (r=0.573), HbA1C% (r=0.515), Flow mediated vasodilatation (r=0.608), serum insulin levels (r=0.511) and HOMA-IR2 levels (r=0.546).

DISCUSSION

A dominant role of NLR was seen in various studies conducted on diabetic patients. Shiny et al.[16] and Lou et al.[17] revealed that increased NLR has strong association with glucose intolerance and insulin resistance in type 2 diabetic patients. Regarding diabetes related micro vascular complications studies showed that NLR has a reliable predictive marker of early stage diabetic nephropathy,[18] retinopathy[19] and diabetic foot ulcer.[20]

In our study, the mean age of the study population was 49.88±10.91 (range = 32.00-78.00) years which co-incided with the findings of *Sefil et al*.,[21]*Fernando et al*.,[22]mean age of diabetic patients in CAD (+) group and CAD (-) group were 59.2±8.05 and 54.56±9.75 respectively and Guo et al.,[23] the mean age was 40.1±13.3 years but was lesser than the findings by *Gubbala et al*,[24] the mean age of the study group was 65.78 years of age.

The gender composition in our study showed more predominance among male when compared to female which is in contrast to study findings of *Sefil et al*[21] but similar to the study finding by *Gubbala et al*[24] and *JinJyu Kim et al*.[25]

In the current study, a positive correlation was found between HbA1c levels and NLR. Also, the relationship was significant for association between the fasting blood sugar levels and NLR.HbA1c levels are an indicator of blood glucose regulation, and increased HbA1c levels may be associated with increased risk of cardiovascular complications in patients with type 2 diabetes mellitus,[26] since impaired glucose tolerance is associated with coronary heart disease.[27] Leukocytes contribute to cholesterol deposition, endothelial dysfunction and atherogenesis.[28]

A positive correlation between HbA1c and WBC levels in patients with type 2 diabetes mellitus[29] was reported in a study that grouped patients according to WBC levels. Another study, in which patients were grouped based on the number of metabolic syndrome components, found a similar correlation between WBC count and HbA1c.[4] In patients with type 2 diabetes mellitus, a link between high WBC levels and impaired insulin sensitivity has been suggested.[30]

Studies by Mertoglu et al. and others showed that higher values of NLR and PLR were associated with

increased high insulin resistence.[31] NLR and PLR were found to be higher in the diabetic group as compared with the control group, which was similar to the findings in this study. A study by *Hussain et al*.[32]found the NLR value to be higher in the poorly controlled diabetics as compared with the well-controlled diabetics which was statistically significant. Moursyet al.[33]showed that NLR and PLR values were significantly higher in diabetic patients with retinopathy and neuropathy than those of diabetic patients without any microvascular complications.

Akbas et al. associated the increased NLR and PLR values in patients with diabetic nephropathy having increased albuminuria.[34]Verdoia et al.[35] reported that increased NLR was related to the severity of coronary artery disease. Aygunet al.[36]found the prevalence of obstructive coronary artery disease to be higher in diabetic patients with NLR >2.05 than those with NLR <2.05.

Shiny et al.[16] compared the NLR value with normal glucose tolerance (NGT), impaired glucose tolerance (IGT) and type 2 diabetes mellitus (DM) and found a significant correlation with IGT and DM. Oh et al.[37] and Demirtas et al.[34] demonstrated association between glycemic control and hematological indices in type 2 diabetic patients and concluded that NLR can be used as a marker of diabetic regulations and complications during the follow up period of diabetic patients.

In a prospective study by Guo X et al.[23]on a nondiabetic 38,074-strong cohort, an average of 6-year follow-up NLR was associated with the incidence and prevalence of T2DM. This result suggests that the NLR is a predictor for the development of diabetes.

Sagar et al.[38]found that there was a significant correlation between NLR and DN, implying that inflammation and endothelial dysfunction could be an integral part of DN. An association between NLR and worsening renal function in diabetic patients has been determined.[39]

Few studies showed a significantly positive association between NLR and FPG in the patients group, while the results of Kim et al.[25]did not show such an association in the IFG/ DM group.

Hyperglycemia increases the release of reactive oxygenspecies from neutrophils, which, in turn, increase vascularendothelial permeability and promote leukocyte adhesion,leading to alterations in endothelial function. Deficiency in theendothelial-derived nitic oxide is also noted. Increased apoptosisin lymphocytes and its increased oxidative DNA damage contributeto its low circulating levels. The insufficient proliferation oflymphocytes due to low expression of IL-2 receptors is also noted.[40]

In our study, there was a significantly positive correlation of NL ratio with Flow mediated vasodilatation. There was a significantly positive correlation of NL ratio with HOMA-IR2 levels.

In accordance with our study, *Shiny et al*.[16]showed that pearson correlation analysis showed a significant positive correlation of NLR with HOMA-IR (*r*=0.233). *Lou et al* reported that NLR values of thediabetic patients were significantly higher than those ofthe healthy control, and the NLR values ofthe patients with a HOMA-IR value of > 2.0 are notablygreater than those of the patients with a HOMA-IRvalue of ≤2.0.

The pathological activation of innate immunity leads toinflammation of the islet cells, resulting in a decrease inpancreatic beta-cell mass and impaired insulin secretion.[41] Patients with T2DM are in a state of low-degreechronic inflammation that induces hypersecretion of inflammatoryfactors, such as CRP, IL-6, TNF-α, andMCP-1, which results in a constantly elevated neutrophilicgranulocyte count.[42]

One mechanism by whichincreased levels of neutrophils could mediate IR maybe through augmented inflammation. The increase inNLR appears to underlie the elevated levels of proinflammation,as evident from the persistent neutrophilactivation and enhanced release of neutrophil proteases with T2DM. Moreover, lymphocytes may bealso associated with inflammation. Some studies haveshown that IR may be related to the signal transductionmediated by T cells and that IR results in a decrease in T-cell count.[43,44]

NLR represents a combination of twomarkers where neutrophils represent the active nonspecificinflammatory mediator initiating the first lineof defense, whereas lymphocytes represent the regulatoryor protective component of inflammation.[45] NLR is superior to other leukocyte parameters (e.g.,neutrophil, lymphocyte, and total leukocyte counts)because of its better stability compared with the otherparameters that can be altered by various physiological,pathological, and physical factors. Thus, as a simpleclinical indicator of IR, NLR is more sensitive comparedwith the neutrophilic granulocyte count and CRP levels,which are widely used as markers of IR.[45]

In contrast, hyperglycemia has been shown to reduce the apoptosis in neutrophils, leading to impaired neutrophil clearance and prolonged inflammation in mice with diabetes.[46]One mechanism by which increased levels of neutrophils could mediate insulin resistance could be through exaggerated inflammation. The increase in NLR appear to underlie the elevated levels of pro-inflammation, as evident from the persistent neutrophil activation and enhanced release of neutrophil proteases in patients with type 2 diabetes.[47]

One of the limitations of this study is that this was a cross-sectional analysis and the sample size was relatively small. Since this was not a prospective controlled study, any conclusive causal associations between NLR and DM could not be investigated.

CONCLUSION

NLR was significantly associated with the diabetic status in the current study. High NLR values may be considered as a predictor and a prognostic risk marker of deteriorating diabetic status. It is one of the simplest parameters to be estimated and calculated in the laboratory on the routine basis. They also have the advantage ofbeing simple andcheap to carry out. They can be easily substituted for expensive inflammatory markers use previously such as ILs, TNF, and cytokines.

REFERENCES

1. Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL. Harrison's principles of internal medicine. 19th ed. Vol. 16. New York: McGraw-Hill; 2015.
2. Centers for Disease Control and Prevention. National Diabetes Fact Sheet: General Information and National Estimates on Diabetes in the United States. Atlanta, GA. US Department of Health and Human Services, Centers for Disease Control and Prevention; 2007.
3. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 2003;26(Supplement 1):S5–20.
4. DallaVestra M, Mussap M, Gallina P, Bruseghin M, Cernigoi A, Saller A, et al. Acute-phase markers of inflammation and glomerular structure in patients with type 2 diabetes. J Am SocNephrol. 2005;16:78–82.
5. Lee G-K, Lee L-C, Chong E, Lee C-H, Teo S-G, Chia B-L, et al. The long-term predictive value of the neutrophil-to-lymphocyte ratio in Type 2 diabetic patients presenting with acute myocardial infarction. QJM. 2012;105(11):1075–82.
6. Ross R. Atherosclerosis is an inflammatory disease. Am Heart J. 1999;138(5):S419–20.
7. Fujita T, Hemmi S, Kajiwara M, Yabuki M, Fuke Y, Satomura A, et al. Complement-mediated chronic inflammation is associated with diabetic microvascular complication. Diabetes Metab Res Rev.2013;29:220–6.
8. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27(5):1047–53.
9. Yuksel M, Yildiz A, Oylumlu M, Turkcu FM, Bilik MZ, Ekinci A, et al. Novel markers of endothelial dysfunction and inflammation in Behçet's disease patients with ocular involvement: epicardial fat thickness, carotid intima media thickness, serum ADMA level, and neutrophil-to-lymphocyte ratio. ClinRheumatol. 2016;35(3):701–8.
10. Tanındı A, Erkan AF, Alhan A, Töre HF. Arterial stiffness and central arterial wave reflection are associated with serum uric acid, total bilirubin, and neutrophil-to-lymphocyte ratio in patients with coronary artery disease. Anatol J Cardiol. 2015;15(5):396–403.
11. Tanındı A, Erkan AF, Ekici B, Alhan A, Töre HF. Neutrophil to lymphocyte ratio is associated with more extensive, severe and complex coronary artery disease and impaired myocardial perfusion. Turk Kardiyol Dern Ars. 2014;42(2):125–30.
12. Lyons TJ, Basu A. Biomarkers in diabetes: hemoglobin A1c, vascular and tissue markers. Translational Res. 1016;2012;159(4):303-312:01 009
13. Lum H, Roebuck KA. Oxidant stress and endothelial cell dysfunction. Am J Physiol Cell Physiol. 2001;280(4):C719-41.
14. Akash MSH, Rehman K, Chen S. Role of inflammatory mechanisms in pathogenesis of type 2 diabetes mellitus. J Cell Biochem. 2013;114(3):525–31.
15. Chung K-P, Chang H-T, Lo S-C, Chang L-Y, Lin S-Y, Cheng A, et al. Severe lymphopenia is associated with elevated plasma interleukin-15 levels and increased mortality during severe sepsis. Shock. 2015;43(6):569–75.
16. Shiny A, Bibin YS, Shanthirani CS, Regin BS, Anjana RM, Balasubramanyam M, et al. Association of neutrophil-lymphocyte ratio with glucose intolerance: an indicator of systemic inflammation in patients with type 2 diabetes. Diabetes TechnolTher. 2014;16(8):524–30.
17. Lou M, Luo P, Tang R, Peng Y, Yu S, Huang W, et al. Relationship between neutrophil-lymphocyte ratio and insulin resistance in newly diagnosed type 2 diabetes mellitus patients. BMC EndocrDisord. 2015;15(1):9.
18. Huang W, Haung J, Liu Q,Lin F, He Z, Zeng Z, et al. Neutrophil -lymphocyte ratio a reliable predictive marker of early stage diabetic nephropathy. ClinEndocrinol. 2015;82(2):229-233.
19. Wang RT, Zhang JR, Li Y, Liu T, Yu KJ. Neutrophil lymphocyte ratio is associated with arterial stiffness in diabetic retinopathy in type 2 diabetes. J Diabetes Complications. 2015;29(2):245-249.
20. Kahraman C, Yumun G, Kahraman NK, Namdar ND, Cosgun S. Neutrophil lymphocyte ratio in diabetes mellitus patients with and without diabetic foot ulcer. Eur J Med Sci. 2014;1:8-13.
21. Sefil F, Ulutas KT, Dokuyucu R, et al. Investigation of neutrophil lymphocyte ratio and blood glucose regulation in patients with type 2 diabetes mellitus. J Int Med Res 2014;42(2):581-8.
22. Fernando ML, Silambanan S, Malar J. Neutrophil to Lymphocyte Ratio as an Indicator of Presence of Coronary Artery Disease in Diabetic Patients. International Journal of Clinical Biochemistry and Research 2015;2(3):143-7.
23. Guo X, Zhang S, Zhang Q, Liu L, Wu H, Du H, et al. Neutrophil:lymphocyte ratio is positively related to type 2 diabetes in a large-scale adult population: a Tianjin Chronic Low-Grade Systemic Inflammation and Health cohort study. Eur J Endocrinol. 2015 Aug;173(2):217-25.
24. Gubbala JC, Thanuj Reddy KV, Prabhakar K. Investigation of neutrophil lymphocyte ratio and blood glucose regulation in patients with type 2 diabetes mellitus. J Evid Based Med Healthc. 2019;6(50):3137-40.
25. Kim JK, Lee AY, Kang JH, et al. Association of fasting glucose level with neutrophil-lymphocyte ratio compared to leukocyte count and serum C – reactive protein. Korean J Fam Med 2018;39(1):42-50.
26. Andersson C, van Gaal L, Caterson ID, et al. Relationship between HbA1c levels and risk of cardiovascular adverse outcomes and all cause mortality in overweight and obese cardiovascular high-risk women and men with type 2 diabetes. Diabetologia 2012; 55:2348–2355.
27. Yousefzadeh P and Wang X. The effects of dipeptidyl peptidase-4 inhibitors on cardiovascular disease risks

in type 2 diabetes mellitus. J Diabetes Res 2013;2013:459–821.
28. 17. Stulc T, Ceska R, Marinov I, et al. The effect of simvastatin and fenofibrate on the expression of leukocyte adhesion molecules and lipopolysaccharide receptor CD14 in type 2 diabetes mellitus. Neuro Endocrinol Lett 2012; 33(suppl 2): 73–77.
29. Tong PC, Lee KF, So WY, et al. White blood cell count is associated with macro and microvascular complications in Chinese patients with type 2 diabetes. Diabetes Care. 2004;27:216-22.
30. Vozarova B, Weyer C, Lindsay RS, et al. High white blood cell count is associated with a worsening of insulin sensitivity and predicts the development of type 2 diabetes. Diabetes 2002;51:455-61.
31. Mertoglu C, Gunay M. Neutrophil-lymphocyte ratio and plateletlymphocyte ratio as useful predictive markers of prediabetes and diabetes mellitus. Diab Met SyndrClin Res Rev 2016;11(1):S127-31.
32. Hussain M, Babar MZM, Akhtar L, Hussain MS. Neutrophil lymphocyte ratio (NLR): A well assessment tool of glycemic control in type 2 diabetic patients. Pak J Med Sci Q. 2017;33(6):1366–70.
33. Moursy EY, Megallaa MH, et al. Relationship Between Neutrophil-Lymphocyte Ratio and Microvascular Complications in Egyptian Patients with Type 2 Diabetes. American J Inter Med 2015;3(6):250-5.
34. Demirtas L, Degirmenci H, Akbas EM, Ozcicek A, Timuroglu A, Gurel A, et al. Association of hematological indicies with diabetes, impaired glucose regulation and microvascular complications of diabetes. Int J ClinExp Med. 2015;8:11420-7.
35. Verdoia M, Shaffer A, et al. Impact of diabetes on neutrophilto- lymphocyte ratio and its relationship to coronary artery disease. Diabetes Metab J 2015;41(4):304-10.
36. Aygün F, Efe D. Association of neutrophil/lymphocyte ratio with obstructive coronary artery disease and coronary artery calcium score detected by multislice computed tomography in type 2 diabetes mellitus patients. *Patient Prefer Adherence*. 2015;9:1023-1031.
37. Oh Y, Kwon GC, Koo SH, Kim J. Association between glycemic control and hematolical indices in type 2 diabetic patients. Laboratory Medicine Online. 2016;6(3):134-13.
38. Sagar A, Sachin C, Nitin N *et al.* (2017): Study of Neutrophil-lymphocyte Ratio as Novel Marker for Diabetic Nephropathy in Type 2 Diabetes, Indian Journal of Endocrinology and Metabolism, 387-392.
39. Azab B, Chainani V, Shah N, McGinn JT. Neutrophil lymphocyte ratio as a predictor of major cardiovascular events among diabetic population: A 4 years follow up study. Angiology. 2013;64(6):456-465.
40. Nagabhushan BK, Geetha JP. Neutrophil– Lymphocyte Ratio and Platelet–Lymphocyte Ratio: Novel Markers in Diabetes Mellitus. J Med Sci 2019;5(2):31–33.
41. Gorasia DG, Dudek NL, Veith PD, Shankar R, Safavi-Hemami H, Williamson NA, Reynolds EC, Hubbard MJ, Purcell AW: Pancreatic Beta Cells Are Highly Susceptible to Oxidative and ER Stresses during the Development of Diabetes J Proteome Res 2014 Dec 8.
42. Tabák AG, Kivimäki M, Brunner EJ, Lowe GD, Jokela M, Akbaraly TN, et al. Changes in C-reactive protein levels before type 2 diabetes and cardiovascular death: the Whitehall II study. Eur J Endocrinol. 2010;163:89–95.
43. Nishimura S, Manabe I, Nagasaki M, Eto K, Yamashita H, Ohsugi M, et al. CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. Nat Med. 2009;15:914–20.
44. Lorenzo C, Hanley AJ, Haffner SM. Differential white cell count and incident type 2 diabetes: the insulin resistance atherosclerosis study. Diabetologia. 2014;57:83–92.
45. Kampoli A-M, Tousoulis D, Briasoulis A, Latsios G, Papageorgiou N, Stefanadis C. Potential pathogenic inflammatory mechanisms of endothelial dysfunction induced by type 2 diabetes mellitus. Curr Pharm Des. 2011;17(37):4147–58.
46. Hanses F, Park S, Rich J, Lee JC. Reduced neutrophil apoptosis in diabetic mice during staphylococcal infection leads to prolonged TNFa production and reduced neutrophil clearance. PLoS One 2011;6:e23633.
47. Hatanaka E, Monteagudo PT, Marrocos MS, Campa A. Neutrophils and monocytes as potentially important sources of proinflammatory cytokines in diabetes. ClinExpImmunol. 2006;146:443–447.