RESEARCH ARTICLE

Correlation of insulin resistance with neutrophil to lymphocyte ratio and serum ferritin in male patients of metabolic syndrome

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Abstract

Objective: To determine the correlation of insulin resistance with neutrophil-to-lymphocyte ratio and serum ferritin, and to evaluate whether NLR and serum ferritin can predict insulin resistance in metabolic syndrome.

Method: The cross-sectional analytical study was conducted at the University of Health Sciences, Lahore, Pakistan, from July 2016 to 2019, and comprised male patients of metabolic syndrome and healthy controls. The correlation involving insulin resistance, serum ferritin and neutrophil-to-lymphocyte ratio was determined. Data was analysed using SPSS 22.

Results: Of the 210 subjects, 160(76.2%) were cases with a median age of 45 years (interquartile range: 39-50 years), and 50(23.8%) were controls with a median age of 41 years (interquartile range: 35-50 years). Serum ferritin, alanine aminotransferase, total neutrophil count, lymphocyte count and neutrophil-to-lymphocyte ratio were significantly higher among the cases than the controls ($p<0.05$). Significant positive correlation of insulin resistance was observed with serum ferritin and neutrophil-to-lymphocyte ratio ($p<0.05$)) among the cases. Neutrophil-to-lymphocyte ratio significantly predicted insulin resistance among the cases ($p<0.05$).

Conclusion: Neutrophil-to-lymphocyte ratio was fund to be a significant predictor of insulin resistance in metabolic syndrome.

Keywords: Neutrophil to lymphocyte ratio, Ferritin, Type 2 diabetes. Insulin resistance. (JPMA 72: 696; 2022)

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Introduction

Metabolic syndrome (MetS) is an emerging global health issue. According to an estimate, about 12-27% of Europeans and 12-36% of Asians are suffering from this derangement.[1] MetS is a cluster of risk factors that significantly increases the probability of coronary heart disease (CHD), cardiovascular accidents and hepatic steatosis. The clinico-biochemical risk factors constituting MetS include central obesity, dyslipidaemia, hypertension (HTN) and impaired glycaemic markers.[2] Insulin resistance (IR) exhibits a fundamental role in the onset and amelioration of MetS pathogenesis. It is described as reduced sensitivity of the target areas of insulin to its actions due to disruption of the signal transduction pathways (STPs).[3] Various studies provide evidence for the crucial role of inflammatory responses in the aetiology of tissue and pathway-specific IR.[4] Neutrophil-to-lymphocyte ratio (NLR), obtained by dividing total neutrophils by the lymphocytes as measured in the complete blood count (CBC), is considered a diagnostic and prognostic marker of inflammation. NLR has been observed to be associated with type 2 diabetes mellitus (T2DM), IR and endothelial dysfunction.[5-7] Serum ferritin, a widely known marker of iron status, is also an indicator of inflammation. A syndrome of dysmetabolic iron overload combines abnormalities such as steatohepatitis, IR and moderate hyperferritinaemia not linked with human leukocyte antigen-A3 (HLA-A3), which is the marker of hereditary hemochromatosis.[8]

The principal manager of iron homeostasis is hepcidin, a 25 amino acid-containing peptide primarily synthesised by the liver in response to elevated ferritin reserves.[9] The relation of hepcidin with ferritin is important as hyperferritinaemia worsens IR and T2DM. Regarding the association between IR, ferritin and hepcidin, two types of results have been documented; IR with raised hepcidin, and IR with low hepcidin levels.[10,11] These evidences are equivocal and there is a scarcity of data from Pakistan regarding the association of the routinely accessible cost-efficient haematological parameters and IR. The current study was planned to determine the relation of IR with NLR and serum ferritin, and to evaluate whether NLR and serum ferritin can predict IR in male MetS patients.

Subjects and Methods

The cross-sectional analytical study was conducted at the University of Health Sciences, Lahore, Pakistan, from July 2016 to 2019. After approval from the institutional ethics review board, the sample size was estimated using the

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World Health Organisation (WHO) calculator opting for hypothesis test for two population means".[11]

Mean values with standard deviation of serum ferritin and NLR were taken from two earlier studies,[12,13] while keeping the level of significance at 5% and power of test 80%.

The sample was raised using convenience sampling technique. Selection of the patients was based on the International Diabetes Federation 2006 guidelines for the diagnosis of MetS[14] which regards central obesity, predicted by waist circumference (WC) >90 cm for men, as an obligatory element of MetS in addition to the presence of any 2 of the following 4 features: fasting plasma glucose (FPG) ≥100mg/dl (5.6mmol/L) or on treatment for T2DM; blood pressure (BP) ≥130/85 or on antihypertensive medicines; fasting high-density lipoprotein (HDL) <40mg/dl (1.03mmol/L) or on lipid-lowering therapy; and fasting triglycerides (TG) ≥150mg/dl (1.7mmol/L) or on lipid-lowering therapy.[14]

Diagnosed cases of MetS were recruited from the Endocrinology and Diabetes Clinic of Sheikh Zayed Hospital, Lahore. A proforma was used to gather the data on disease history, demographics, clinical and biochemical parameters. Available reports and investigations with the subjects were scrutinised. All those already taking antihypertensive or lipid-lowering agents were considered to be dyslipidaemic or hypertensive irrespective of their present status. Age-matched male controls were taken from among the hospital staff and non-blood-related attendants of out-patients.

Those excluded were cases of MetS taking iron or vitamin preparations for the preceding 6 months, having evidence of deranged serum creatinine or renal impairment, acute or chronic infections or secondary causes of T2DM.

After taking informed consent from all the participants, BP and WC were measured using the standard methods. A fasting venous blood sample of 8ml was taken and the serum was separated to measure biochemical parameters. Serum insulin, ferritin and hepcidin were measured using enzyme-linked immunosorbent assay (ELISA) (Amgenix International, USA, kit for insulin; Chemux Bioscience, Inc South San Francisco, kit for ferritin, and International Immunodiagnostics, USA, for hepcidin). Serum TG, (HDL), and glucose were measured by colorimetric method (Randox Kit, United Kingdom). IR was calculated by homeostatic model assessment for insulin resistance (HOMA-IR) using the equation; HOMA-IR = FPG (mmol/L) x fasting insulin (μ IU/ml)/22.5.[15]

Haemoglobin (Hb) and blood cell counts were measured by automated haematology analyser. NLR was calculated by dividing total neutrophils with the lymphocyte count.

Data was analysed using SPSS 22. Normality of data was assessed using Shapiro-Wilk's test and it was found to be non-normally distributed. Median with interquartile range (IQR) was used to present the data, and Mann-Whitney U test was used for comparison of variables between the groups. P<0.05 was taken as a mark of statistical significance. Correlation between the study variables was determined by Spearman test as the data was non-normally distributed. Stepwise linear regression analysis was applied to control all the covariates statistically, and to determine the independent covariates that can significantly predict the dependent variable HOMA-IR. Receiver operating characteristic (ROC) curve was generated to determine the cut-off levels of the significant predictors of HOMA-IR from area under the curve (AUC). Sensitivity and specificity were calculated to find out the diagnostic accuracy of the significant predictors of HOMA-IR.

Results

Of the 210 subjects, 160(76.2%) were cases with a median age of 45 years (IQR: 39-50 years), and 50(23.8%) were controls with a median age of 41 years (IQR: 35-50 years) (p>0.05). All (100%) MetS patients were diabetic, 91(83%)

Table-1: Comparison of clinical and biochemical parameters between the study groups.

Study parameters	Metabolic syndrome Median (IQR)	Healthy subjects Median (IQR)	*p-value
Age (years)	45 (39-50)	41 (35-50)	0.10
Systolic BP (mm of mercury)	130 (110-140)	120 (110-130)	0.00*
Diastolic BP (mm of mercury)	80 (70-90)	80 (70-80)	0.02*
Waist circumference (cm)	100 (92-105)	80 (74-86.25)	0.000*
Serum HDL (mg/dl)	38 (31-44)	39 (37-44)	0.08
Serum triglycerides (mg/dl)	209 (153-290)	150 (135-190)	0.00*
Plasma glucose (mg/dl)	140 (118-190)	90 (80.75-98.5)	0.000*
Serum insulin (μIU/ml)	24.6 (14.4-45.59)	8.7 (5.8-12.3)	0.000*
HOMA-IR	9.45 (6-20)	1.99 (1.3-3.2)	0.000*
Serum ALT (IU/L)	32.5(24-45.2)	26 (18-36)	0.00*
Serum ferritin (ng/ml)	75.5(29-159)	21.5 (11.7-39.5)	0.000*
Serum hepcidin (μg/L)	39 (28-47.8)	54 (32.7-85.9)	0.000*
Haemoglobin (gm/dl)	13.95 (12.7-14.7)	14.75 (14-15.5)	0.000*
Red cell count $x10^6$/μL	5 (4.5-5.3)	5.1 (4.7-5.3)	0.44
Total leucocyte count $x10^3$/μL	9 (8.1-10.6)	7.5 (6.2-9.2)	0.000*
Neutrophil count $x10^3$/μL	5.7 (4.6-7.3)	4.5 (3.5-6)	0.000*
Lymphocyte count $x10^3$/μL	2.6 (2.1-3.7)	2.3 (2.1-2.8)	0.02*
Neutrophil to lymphocyte ratio	2.2 (1.7-2.9)	1.5 (1.3-1.9)	0.02*

IQR: Interquartile range, BP: Blood pressure, HDL: High-density lipoprotein, HOMA-IR: Homeostatic model assessment for insulin resistance, ALT: Alanine aminotransferase. Values are expressed as median (interquartile range). A p of less than 0.05 is statistically significant.

Table-2: Correlation of HOMA-IR with the study parameters.

Study parameters	Waist circumference	Neutrophil to lymphocyte ratio	Serum ferritin	Serum hepcidin	Serum alanine aminotransferase
Correlation of HOMA-IR in metabolic syndrome					
Rho (p-value)	0.25 (0.01*)	0.21 (0.03*)	0.27 (0.005*)	0.27 (0.01*)	0.00 (0.97)
Correlation of HOMA-IR in healthy group					
Rho (p-value)	0.55 (0.000*)	0.16 (0.28)	0.29 (0.04*)	0.13 (0.36)	0.16 (0.26)

Spearman correlation was applied to see the relation between quantitative variables. A "p" of less than 0.05 is statistically significant*.
HOMA-IR: Homeostatic model assessment for insulin resistance.

Table-3: Significant predictors of HOMA-IR by regression analysis in metabolic syndrome.

Independent variables	Median (IQR) Mean±SD	B coefficient	95% confidence interval	t	p-value
Systolic BP (mm of mercury)	130 (110-140) 124.67±14.96	0.024	-0.794	0.121	0.904
Diastolic BP (mm of mercury)	80 (70-90) 80.78±10.07	0.105	-1.189	0.349	0.728
Waist circumference (cm)	100 (92-105) 101.24±13.02	0.047	-0.583	0.318	0.751
Serum HDL (mg/dl)	38 (31-44) 38.25±8.90	-0.121	-0.819	-0.588	0.558
Serum triglycerides (mg/dl)	209 (153-290) 235.34±126.54	-0.003	-0.059	-0.235	-0.815
Serum ALT (IU/L)	32.5 (24-45.2) 40.61±27.37	0.057	-0.303	0.744	0.459
Serum ferritin (ng/ml)	75.5 (29-159) 111.61±90.62	0.003	-0.077	0.149	0.882
Serum hepcidin (µg/L)	39 (28-47.8) 40.75±21.52	-0.04	-0.387	-0.43	0.668
Neutrophil count x10^3/µL	5.7 (4.6-7.3) 5.89±2.32	-0.72	-3.17	-0.901	0.37
Lymphocyte count x10^3/µL	2.6 (2.1-3.7) 2.67±0.73	2.785	-11.394	0.97	0.334
Neutrophil to lymphocyte ratio	2.2 (1.7-2.9) 2.67±2.19	4.566	2.452-6.680	4.28	0.000*

SD: Standard deviation, IQR: Interquartile range, BP: Blood pressure, HDL: High-density lipoprotein, HOMA-IR: Homeostatic model assessment for insulin resistance, ALT: Alanine aminotransferase.

were hypertensive and 102(93%) had dyslipidaemia. Serum ferritin, alanine aminotransferase (ALT), total neutrophil count, lymphocyte count and NLR were significantly higher (p<0.05) among the cases than the controls (Table-1). Median Hb and serum hepcidin levels were significantly lower (p=0.000) among the case compared to the controls, and there was no significant difference regarding red blood cell (RBC) count between the groups (p>0.05).

There was significant positive correlation of HOMA-IR with serum ferritin (p=0.005) and NLR (p=0.031) in MetS. There was also significant positive correlation of serum ferritin with WC (p=0.00), NLR (p=0.00), serum hepcidin (p=0.01) and serum ALT (p=0.000) in MetS (Table-2). Among the controls, there was significant correlation of HOMA-IR with serum ferritin (p=0.04), while no significant correlation was found between

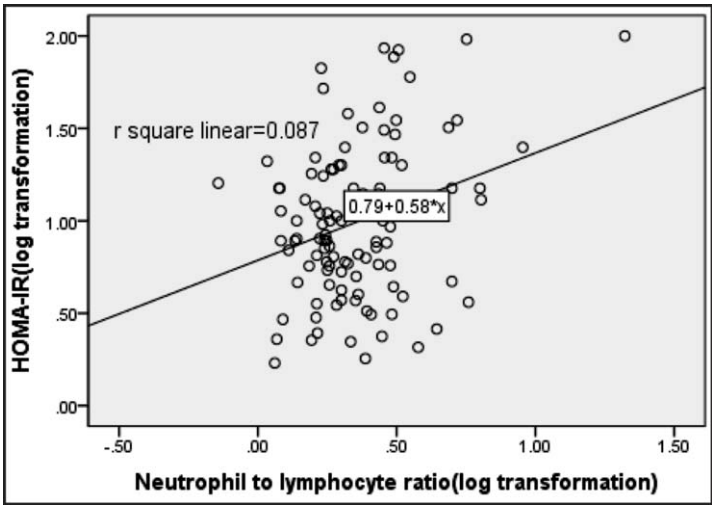

Figure-1: Scatter-plot showing relationship between neutrophil to lymphocyte ratio and homeostatic model assessment for insulin resistance (HOMA-IR).

Table-4: Significant predictors of HOMA-IR by regression analysis in the healthy group.

Independent variables	Median (IQR) Mean±SD	B coefficient	95% confidence interval	t	p-value
Systolic BP (mm of mercury)	120 (110-130) 117±13.85	0.065	-0.397	0.658	0.514
Diastolic BP (mm of mercury)	80 (70-80) 76.30±8.79	-0.16	-0.621	-1.046	0.302
Waist circumference (cm)	80 (74-86.25) 81.2±9.26	0.363	0.069-0.656	2.502	0.017*
Serum HDL (mg/dl)	39 (37-44) 40.58±6.39	-0.162	-0.614	-1.067	0.293
Serum triglycerides (mg/dl)	150 (135-190) 181.12±97.10	-0.017	-0.039	0.006	0.139
Serum ALT (IU/L)	26 (18-36) 28.35±13.78	0.031	-0.353	0.36	0.721
Serum ferritin (ng/ml)	21.5 (11.7-39.5) 48.98±26.92	0.046	0.017-0.074	3.26	0.002*
Serum hepcidin (µg/L)	54 (32.7-85.9) 56.99±28.83	-0.061	-0.133	-0.183	0.074
Neutrophil count x10^3/µL	4.5 (3.5-6) 4.65±1.84	-0.937	-2.052	-0.185	0.072
Lymphocyte count x10^3/µL	2.3 (2.1-2.8) 2.52±0.57	0.395	-6.701	0.239	0.813
Neutrophil to lymphocyte ratio	1.5 (1.3-1.9) 1.69±0.63	0.578	-6.342	0.369	0.714

SD: Standard deviation, IQR: Interquartile range, BP: Blood pressure, HDL: High-density lipoprotein, HOMA-IR: Homeostatic model assessment for insulin resistance, ALT: Alanine aminotransferase.

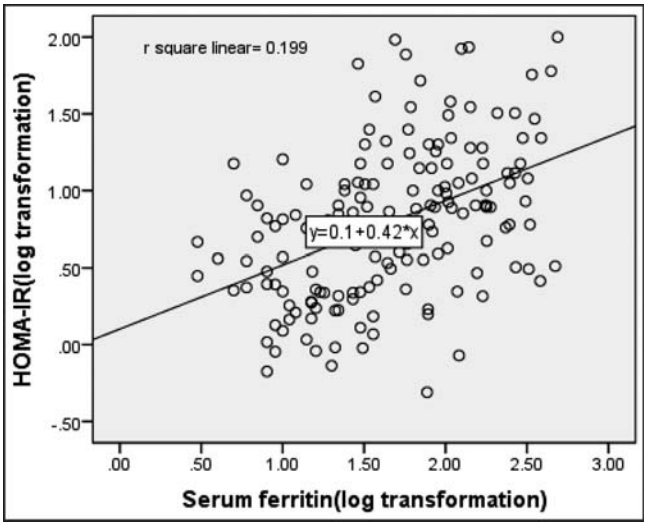

Figure-2: Scatter-plot showing relationship between serum ferritin and homeostatic model assessment for insulin resistance (HOMA-IR).

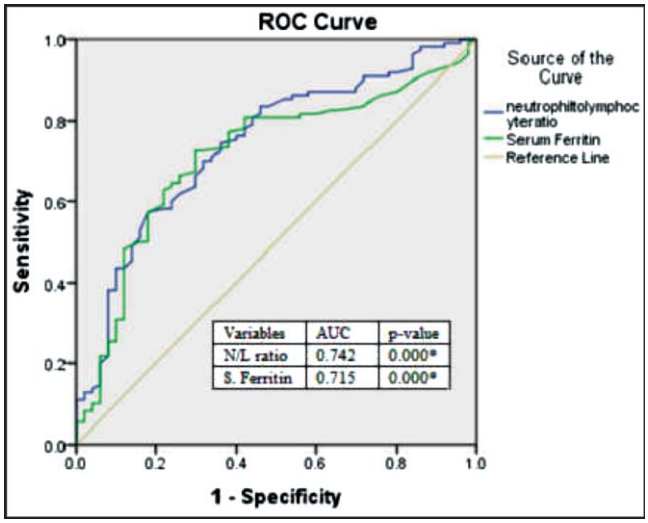

Figure-3: Receiver operating characteristic (ROC) curve showing area under the curve for neutrophil-to-lymphocyte ratio (NLR) and serum ferritin.

NLR serum ferritin and other parameters (Table-3).

On stepwise linear regression analysis after controlling all the independent confounder variables, covariate that significantly predicted the dependent variable HOMA-IR in MetS was NLR and WC, whereas among the controls, significant predictor of HOMA-IR was serum ferritin (T 4; Figure-1,2).

ROC curve depicted significant AUC for NLR and serum ferritin (Figure-3). The cut-off level of NLR was 1.7, with sensitivity 74.5% and specificity 66%. The cut-off level of serum ferritin was 33.5ng/ml with sensitivity 71% and specificity 70%.

Discussion

The current study aimed at determining the correlation of IR with NLR and serum ferritin, and to evaluate whether these parameters could be utilised to predict IR as well.

The study found significant positive correlation between HOMA-IR and NLR among the MetS cases, and, on stepwise linear regression analysis after controlling all the covariates, NLR was found to be the significant independent determinant of IR in MetS. With ROC curve statistics, although the cut-off level (1.7) of NLR for prediction of IR exhibited 74.5% sensitivity and 66% specificity, AUC for NLR was acceptable and significant. Significant correlation of NLR was found with WC and serum ferritin in MetS, but the study was unable to find significant relationship between neutrophil count and HOMA-IR. Results of the present study are in concordance with those of preceding studies.[16,17] A retrospective observational study on MetS patients at Mackay Memorial Hospital, Taipei, Taiwan, revealed that NLR can be utilised as a cost-effective tool to predict MetS as the risk of MetS was found to increase with the increasing NLR.[16] Another study on T2DM patients with MetS reported NLR as an independent predictor of MetS.[17]

The value of NLR in the present study in the control population was comparable to the reference value of NLR 1.76 (0.83-3.92) reported from a prospective population-based cohort study conducted in the Rotterdam, the Netherlands.[18] In a study on obese type 2 diabetics, ROC curve analysis revealed that NLR of more than 3.12 was 79.2% sensitive and 64.9% specific for predicting T2DM.[19] A study among type 2 diabetic Indians revealed that NLR of 2 had 86.4% sensitivity and 69% specificity in predicting albuminuria, and 64.2% sensitivity and 63% specificity in predicting retinopathy.[20] A study on biopsy-proven cases of non-alcoholic steatohepatitis (NASH) proclaimed higher values for NLR in NASH patients compared to those without it.[21] Although blood leucocyte and platelet-based indices, such as NLR and platelet-to-lymphocyte ratio (PLR) have been used as sensors of inflammation and prognostic markers for various metabolic derangements, a study on MetS subjects without diabetes showed that NLR was not a good sensor of inflammation, and total neutrophil count and C-reactive protein (CRP) were more useful parameters of inflammation.[13]

In the present study, serum ferritin was significantly higher in MetS cases compared to the controls and a significant positive correlation was also observed between ferritin and IR. There is 10-15-fold variation in normal serum ferritin level; ranging 30-300ng/ml for males and 15-200ng/ml for females.[22] Though in the current study, median ferritin (75.5ng/ml) was within the reference range, it was significantly higher in cases compared to controls. There was a relative ferritin overload in MetS and a significant positive correlation of ferritin was also observed with WC, ALT and HOMA-IR.

The conditional or relative hyperferritinaemia in the cases reflected underlying hepatic inflammation and steatosis rather than the iron overload. This finding is consistent with the diagnosis of IR-related hepatic iron overload and NASH.[23] Due to hepatic IR ability of insulin to suppress lipolysis, and the release of very low-density lipoproteins (VLDL) is impaired which leads to increased hepatic accumulation of fatty acids and TGs. As a consequence of chronic IR-induced inflammation in the liver, synthesis of interleukin-6 (IL-6) is increased, causing the release of ferritin from the damaged hepatocytes.[22] A significant association of serum ferritin with IR syndrome was also observed in a representative German population and South Korean adults.[24,25]

In the current study, serum hepcidin was significantly lower in MetS compared to the controls. This finding is in concordance with a study that reported decreased messenger ribonucleuc acid (mRNA) of hepcidin in liver in IR and T2DM.[10] It has been observed that diminished hepatic insulin signalling due to IR decreases the production of hepcidin by downregulating signal transducer and activator of transcription 3 (STAT3)-mediated pathways.[26]

In the current study, serum ferritin was significantly higher, but serum hepcidin was significantly lower in MetS compared to the healthy group, but positive correlation was observed between serum ferritin and hepcidin in type 2 diabetics, depicting a normal iron homeostasis. The correlation between the two parameters might be mediated by the parallel release of hepcidin along with insulin from the beta cells of pancreas due to glucose stimulation or increased IL-6 and inflammatory cytokine production by the liver.[9]

Though the current study observed significant correlation of HOMA-IR with NLR and serum ferritin, there are certain limitations to the study. Due to the cross-sectional study design, the current evidence has limited ability to provide cause-effect relation. It also did not consider other markers of inflammation and metabolic liver disease, such as CRP, gamma glutamyl transferase (GGT) and histological evidence of hepatic steatosis in MetS. Moreover, only male subjects were included. Future studies may enlarge the scope by involving female patients and confirmed cases of hepatic steatosis to evaluate the relationship of IR and inflammation with haematological markers, such as NLR and ferritin.

Conclusion

NLR was found to be a significant predictor of IR in male

MetS patients.

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References

1. Sigit FS, Tahapary DL, Trompet S, Sartono E, van Dijk KW, Rosendaal FR, et al. The prevalence of metabolic syndrome and its association with body fat distribution in middle-aged individuals from Indonesia and the Netherlands: a cross-sectional analysis of two population-based studies. Diabetol Metab Syndr 2020; 12:2.
2. Liu J, Grundy SM, Wang W, Smith SC Jr, Vega GL, Wu Z, et al. Ethnic-specific criteria for the metabolic syndrome: evidence from China. Diabetes Care. 2006; 6:1414-6.
3. Yaribeygi H, Farrokhi FR, Butler AE, Sahebkar A. Insulin resistance: Review of the underlying molecular mechanisms. J Cell Physiol. 2018; 234:8152-61.
4. Rehman K, Akash MSH. Mechanisms of inflammatory responses and development of insulin resistance: how are they interlinked? J Biomed Sci. 2016; 23: 87.
5. 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 Endocr Disord. 2015; 15:9.
6. Surendar J, Indulekha K, Mohan V, Pradeepa R. Association of neutrophil lymphocyte ratio with metabolic syndrome and its components in Asian Indians (CURES- 143). J Diabetes Complications. 2016; 30:1525-9.
7. Martínez-Urbistondo D, Beltrán A, Beloqui O, Huerta A. The neutrophil–lymphocyte ratio as a marker of systemic endothelial dysfunction in asymptomatic subjects. Nefrología. 2016; 36:397-403.
8. Jin Y, He L, Chen Y, Fang Y, Yao Y. Association between serum ferritin levels and metabolic syndrome: an updated meta-analysis. Int J Clin Exp Med. 2015; 8:13317-22.
9. Lwanga SK, Lemeshow S. Sample size determination in health studies: a practical manual: Geneva: World Health Organization, 1991; pp-80.
10. Aregbesola A, Voutilainen S, Virtanen JK, Aregbesola A, Tuomainen TP. Serum hepcidin concentrations and type 2 diabetes. World J Diabetes. 2015; 6:978-82.
11. Wang H, Li H, Jiang X, Shi W, Shen Z, Li M. Hepcidin is directly regulated by insulin and plays an important role in iron overload in Streptozotocin-induced diabetic rats. Diabetes. 2014; 63:1506-18.
12. Wolide AD, Zawdie B, Alemayehu T, Tadesse S. Evaluation of serum ferritin and some metal elements in type 2 diabetes mellitus patients: comparative cross-sectional study. Diabetes Metab Syndr Obes. 2016; 9:417-24.
13. Bahadır A, Baltacı D, Turker Y, Turker Y, Iliev D, Ozturk S, et al. Is the neutrophil-to-lymphocyte ratio indicative of inflammatory state in patients with obesity and metabolic syndrome? Anatol J Cardiol. 2015; 15:816-22.
14. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. Circulation. 2009; 120:1640-5.
15. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985; 28: 412-9.
16. Liu CC, Ko HJ, Liu WS, Hung CL, Hu KC, Yu LY, et al. Neutrophil-to-lymphocyte ratio as a predictive marker of metabolic syndrome. Medicine (Baltimore) 2019; 98: e17537.
17. Kaya T, Solak Y, Akcay EU, Erturk Z, Ergenç H, Tamer A. The relationship between neutrophil to lymphocyte ratio and metabolic syndrome in patients with type 2 diabetes.Int J Diabetes Dev Ctries. 2017; 3:215-20.
18. Fest J, Ruiter R, Ikram MA, Voortman T, van Eijck CH, Stricker BH. Reference values for white blood-cell-based inflammatory markers in the Rotterdam Study: a population-based prospective cohort study. Sci Rep. 2018; 8:1-7.
19. Yilmaz H, Ucan B, Sayki M, Unsal I, Sahin M, Ozbek M, et al. Usefulness of the neutrophil-to-lymphocyte ratio to prediction of type 2 diabetes mellitus in morbid obesity. Diabetes Metab Syndr. 2015; 9:299-304.
20. Chittawar S, Dutta D, Qureshi Z, Surana V, Khandare S, Dubey TN. Neutrophil-lymphocyte ratio is a novel reliable predictor of nephropathy, retinopathy, and coronary artery disease in Indians with type-2 diabetes. Indian J Endocr Metab. 2017; 21:864-70.
21. Paquissi FC. Immune imbalances in non-alcoholic fatty liver disease: from general biomarkers and neutrophils to interleukin-17 axis activation and new therapeutic targets. Front Immunol 2016; 7: 490.
22. Simcox JA, McClain DA. Iron and diabetes risk. Cell Metab. 2013; 17: 329-41.
23. Brudevold R, Hole T, Hammerstrom J. Hyperferritinemia is associated with insulin resistance and fatty liver in patients without iron overload. PLoS One. 2008; 3:e3547.
24. Wrede C, Buettner R, Bollheimer L, Scholmerich J, Palitzsch K, Hellerbrand C. Association between serum ferritin and the insulin resistance syndrome in a representative population. Eur J Endocrinol. 2006; 154:333-40.
25. Shim YS, Kang MJ, Oh YJ, Baek JW, Yang S, Hwang IT. Association of serum ferritin with insulin resistance, abdominal obesity, and metabolic syndrome in Korean adolescent and adults: The Korean National Health and Nutrition Examination Survey, 2008 to 2011. Medicine (Baltimore). 2017; 96: e6179.
26. Vela D, Leshoski J, Gjorgievska ES, Hadzi-Petrushev N, Jakupaj M, Sopi RB, et al. The role of insulin therapy in correcting Hepcidin levels in patients with type 2 diabetes mellitus. Oman Med J. 2017; 32:195-200.