Original Article

Correlation of Neutrophil-to-Lymphocyte Ratio with Waist Circumference, Insulin Resistance and Lipid Profile in Metabolic Syndrome and Healthy Controls

Fareena Ahmad[1], Hafiz Abdul Rehman Tariq[2], Nida Zubair[3], Huma Saeed Khan[1]

[1]Department of Physiology, University of Health Sciences, Lahore; [2]Specialized Health Care & Medical Education Department affiliated with University of Health Sciences, Lahore; [3]Department of Physiology, Shalimar Medical & Dental College affiliated with University of Health Sciences, Lahore

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Abstract

Background: Metabolic syndrome encompasses a spectrum of interconnected derangements, such as central adiposity, dyslipidemia, insulin resistance and high blood pressure. Low-grade chronic inflammation has a major contribution in the onset and progress of metabolic syndrome. The neutrophil-to-lymphocyte ratio is a well-recognized predictive index for various inflammatory disorders.

Objective: To determine the correlation of neutrophil to lymphocyte ratio with insulin resistance, waist circumference, serum triglycerides and high-density lipoproteins in metabolic syndrome and healthy group.

Methodology: This was a cross-sectional study undertaken at University of Health Sciences Lahore, from October 2019 to September 2022. Approval was obtained from the Ethical Board of the University of Health Sciences. . The subject recruitment was from the Endocrine and Diabetes Clinic of Sheikh Zaid Institute, Lahore. Anthropometric measures and biochemical variables were determined. Data was analyzed by the software; SPSS 27.

Results: The present study comprised of 90 patients diagnosed with metabolic syndrome and 50 controls. In both groups, only male patients were present. The median (IQR) age of the participants with and without metabolic syndrome was found to be 44(40-49.5) and 41(43-49) respectively. The waist circumference, systolic as well as diastolic blood pressure was higher substantially in metabolic syndrome group compared with the healthier ($p<0.001$). Fasting serum glucose, insulin and triglycerides showed a significant difference among both groups statistically ($p<0.001$). There was a positive correlation of neutrophil to lymphocyte ratio with waist circumference ($p=0.006$) and HOMA-IR ($p=0.005$) in metabolic syndrome group and significant inverse relation with high density lipoproteins ($p=0.007$) in healthier ones.

Conclusion: The positive correlation of neutrophil to lymphocyte ratio with insulin resistance and waist circumference in metabolic syndrome highlights the role of chronic inflammation in the disease process.

Keywords: Neutrophil to lymphocyte ratio, Insulin resistance, Chronic inflammation

Correspondence:
Fareena Ahmad, *Department of Physiology, University of Health Sciences, Lahore. Email: Fareenaahmad1988@gmail.com*

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Introduction

Metabolic syndrome (MetSy) a complex multifaceted disorder is characterized by a spectrum of interconnected derangements, such as central adiposity, dyslipidemia, insulin resistance and

high blood pressure. It profoundly increases the susceptibility to heart diseases and diabetes type2. As a non-infectious chronic disease, prevalence of MetSy in Pakistan is 33%. Its pooled burden in South Asian region ranges between 17 to 32.5% whereas its global burden is 25 %.[1,2] Low-grade chronic inflammation by disrupting normal metabolic pathways has a major contribution in the onset and progress of MetSy. Prolonged inflammation drives adipose dysfunction that leads to oxidative radical stress, insulin non-responsiveness and disseminated inflammation. Insulin resistance has a prime role in ignition and progression of metabolic dysregulation. Multiple pathological derangements, including imbalance in hepatic lipid and glucose homeostasis, excess free fatty acids (FFAs) release from adipose organs, impaired skeletal glucose uptake, and disrupted pancreatic insulin secretion, contribute to the initiation of central adiposity or insulin resistance. Resistance to insulin action in adipose organs promotes lipolysis resulting in release of free fatty acids. These agents result in lipid accumulation in liver, which selectively hampers insulin action. This results in dyslipidemia picture with elevated triglycerides and low high-density lipoproteins (HDL) in the blood. Disruption of insulin signaling pathways are mainly responsible for non-responsiveness of target areas to insulin action.[3,4]

Many studies underscore the role of inflammation in tissue or area related insulin non-responsiveness. The neutrophil-to-lymphocyte ratio (NLR) is a well-recognized predictive index for various inflammatory disorders.[5] Neutrophil activation contributes to the recruitment of diverse cell types involved in both acute and chronic inflammation, affecting outcome of disease. Neutrophilic to lymphocytic ratio obtained after dividing total neutrophil count by lymphocyte count as given in blood report has emerged as an early marker for diagnosis and prediction of MetSy.[6] Higher NLR level has been observed in insulin resistance endorsing it a state of subclinical inflammation. Previous studies have reported higher NLR values in diabetic patients with a greater likelihood of insulin resistance.[7]

Comprehending inflammation as a root cause of MetSy may navigate the way for precise therapeutic trials aimed at lowering inflammation and elevating metabolic health. As a cost-efficient inflammatory marker, NLR carries potential for the preliminary prediction of MetSy.

The objective of this study was to determine the correlation of NLR with insulin resistance, waist circumference, serum triglycerides and high-density lipoproteins in MetSy and healthy group.

Methodology

This was an analytical and cross-sectional study undertaken at University of Health Sciences Lahore from October 2019 to September 2022.

Ethical consideration: Approval was obtained from the Ethical Board of the University of Health Sciences [UHS/REG-19/ERC/3219] Dated: 29/11/2021. Informed written consent was obtained from the participants, and the confidentiality of their data was clearly explained.

This study included 140 subjects. Calculation of sample size was done with the following equation from WHO calculator.

$$n_1 = \frac{\left(Z_{1-\beta} + Z_{1-\frac{\alpha}{2}}\right)^2 (\sigma_1^2+\sigma_2^2)}{(\mu 1-\mu 2)^2}$$

Z1-β is the power of study 90% and Z 1-α/2 is level of significance 0.05

Minimum sample size was 50 for each group. In the present study, there were 90 cases of metabolic syndrome (Group A) and 50 controls (Group B)

The sampling technique of convenience sampling was adopted. The subject recruitment was from the Endocrine and Diabetes Clinic of Sheikh Zaid Institute, Lahore. The MetSy cases were selected in line with IDF (International Diabetes Federation) criteria . The medical record of the recruiter was evaluated for other concomitant ailment. There are different criteria for the determination of MetSy.

Inclusion Criteria:

As per the rules of IDF, MetSy is present if a subject has central obesity reflected by waist circumference ≥90cm in men, triglycerides ≥1.7 mmol/L or on specific lipid lowering drugs; HDL-cholesterol level ≤1.03 mmol/L in males; elevated blood pressure ≥130/85 or on antihypertensive; fasting plasma glucose ≥5.6 mmol/L or taking anti-diabetics.[8]

Exclusion criteria:

All those cases of MetSy were excluded who had evidence of any of the infectious and inflammatory state such as chronic liver disease, end-stage renal disease, chronic infection or malignancies. Controls were non-blood related attendants of the cases or healthy subjects of hospital.

After getting the written informed consent, every subject was assessed. Blood pressure and waist circumference was recorded by the standard method . Waist circumference (in centimeters) was measured in a horizontal plane midway between the costal margin and iliac crest at the end of normal expiration by a non-stretchable measuring tape.[9] Patients with overnight fast of 8 to 10 hours were counselled for collection of blood sample of 5 ml. Sample was collected in vacutainers of 5 ml and and serum was extracted in the laboratory. It was stored at -400C. Serum insulin levels were measured by Enzyme-Linked Immunosorbent Assay (ELISA) kit (Bio-Rad Laboratories, Hercules, CA, USA). Fasting blood glucose was measured by glucometer. Serum triglycerides and HDL were estimated with the corresponding kits by the colorimetric method (Randox kit). Insulin resistance was calculated by homeostatic model assessment for insulin resistance (HOMA-IR) using following equation.[10]

HOMA-IR=(Fasting plasma glucose (mmol/l)× Fasting plasma insulin (mU/l))/22.5

Statistical Analysis

The data was analyzed by SPSS 27 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp). To assess the data distribution, Shapiro-Wilk's stats for normality was conducted. Data distribution was skewed as p-value was less than 0.05. Study variables were summarized as median showing central tendency along with interquartile range (IQR) showing dispersion. Non-parametric comparison tests the Wilcoxon Rank Sum was used to compare continuous parameters. Spearman correlation was employed to measure the correlation of continuous quantitative variables. A p of less than 0.05 was of statistical significance.

Results

The present study comprised of 90 patients diagnosed with MetSy and 50 controls. In both groups, only male patients were present. The median (IQR) ages of the group of patients with and without MetSy were found to be 44(40-49.5) and 41(43-49) respectively. The systolic as well as diastolic blood pressure was higher substantially in the cases of MetSy compared with the healthier ones (p<0.001). The median values of waist circumference was higher in cases compared to the controls. Fasting median serum glucose, insulin, triglycerides, had shown a significant difference among both groups. Comparison of study variables in given in Table-I.

Table I: *Comparison of study variables between metabolic syndrome and healthy group*

Study variables	Metabolic syndrome	Healthy group	p-value
	n= 90	n=50	
Age	44 (40-49.75)	41 (34-49)	0.08
Waist circumference in cm	99 (93-106)	84 (75-88)	<0.001*
Serum glucose in mg/dl	142 (120-176)	90 (80-99)	<0.001*
Serum insulin in µI U/ml	22 (12.95-33.6)	8.8 (6-13.5)	<0.001*
HOMA-IR	6.35 (3.97-10)	1.79 (1.27-3.04)	<0.001*
Total leucocyte count X 10^3 /µL	8.85 (7.27-10.30)	7.34 (6.15-8.23)	<0.001*
Total neutrophil count X 10^3 /µL	5.5 (4.1-6.92)	4.4 (3.5-4.9)	0.001*
Total lymphocyte count X 10^3/µL	2.5 (2.0-3.9)	2.2 (1.9-2.9)	0.062
Neutrophil to lymphocyte ratio	2.29 (1.82-3)	1.76 (1.52-2.32)	0.005*
Serum triglycerides in mg/dl	213 (161-203)	150 (135-190)	0.001*
Serum HDL in mg/dl	37.5 (31-43.2)	39 (35-46)	0.062

The p-value is determined by Wilcoxon Rank sum test. A value less than 0.05 is of significance statistically. (n= number of participants)

There were positive correlational results of NLR with waist circumference and HOMA-IR in MetSy group and a significant inverse relation with HDL in healthier ones. (Table II and Figures I & II)

Table II: *Correlation of neutrophil to lymphocyte ratio with study variables*

	HOMA-IR	Waist circumference	Serum triglycerides	Serum HDL
Correlation of neutrophil to lymphocyte ratio with study variables in metabolic syndrome group				
Rho value	0.289	0.285	0.145	0.168
p-value	0.005*	0.006*	0.477	0.335
Correlation of neutrophil to lymphocyte ratio with study variables in healthy group				
Rho value	0.245	0.14	0.022	-0.378
p-value	0.08	0.332	0.14	0.007*

The p-value is determined by Spearman test. A value less than 0.05 is of significance statistically.

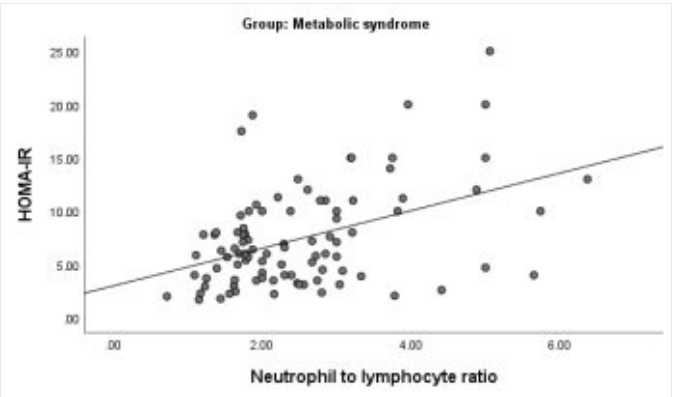

Figure-I: *Correlation of neutrophil to lymphocyte ratio with HOMA-IR in metabolic syndrome.*

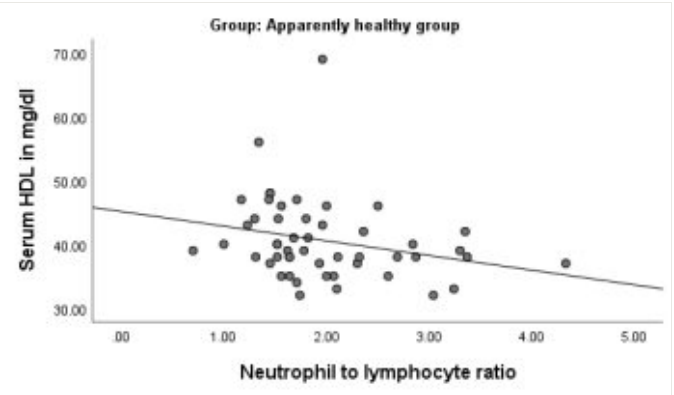

Figure-II: *Correlation of neutrophil to lymphocyte ratio with serum HDL in healthy group*

Discussion

The present study revealed considerably higher NLR, insulin resistance, and waist-circumference in cases as compared to the controls. Furthermore, NLR was positively related with insulin resistance and waist circumference in the diseased group. These results are in agreement with the previous studies conducted in Pakistan and neighboring areas.[6,7,11] The current study is conducted on male patients only, however a study conducted in patients with gestational diabetes also revealed considerable association of NLR with insulin resistance and body mass index.[12] Another previous study observed relationship between new measures of inflammation such as NLR, platelet count, neutrophil count and insulin resistance in obese children. Increased leucocyte count and elevated NLR in obese or overweight boys serve as biomarker of insulin resistance and were endorsed to be undertaken when evaluating the risk of potential complications, such as type 2 diabetes mellitus.[13] A systematic review revealed the relation of NLR with poorly controlled glycated hemoglobin in type2 diabetics. NLR was considerably higher in the group exhibiting poor control of glycosylated hemoglobin as compared to the one with good control.[14] Another study revealed that NLR correlated positively with HbA1C in type2 diabetics.[15] These studies reflect that insulin resistance and hyperglycemia lead to oxidative stress thus contributing towards chronic inflammation; which in turn results in neutrophilia and relative fall in lymphocytic count. There are various postulated mechanisms, by which insulin resistance leads to immune dysregulation. The mechanisms include release of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor, which promote production of neutrophils.[16,17] Increased waist circumference is a prime indicator of central obesity and is correlated strongly with insulin resistance and chronic low-grade inflammation. Visceral fat being a dynamic endocrine organ, release pro-inflammatory cytokines (e.g., TNF-α, IL-6, visfatin), which increases neutrophil production and reduce lymphocyte count, leading to an elevated NLR.[18,19] Central obesity is also linked to poor glycemic control, contributing to higher HbA1c levels. An increasing level of NLR indicate worsening of glucose regulation and risk of cardiovascular complications.[20-22] This relation underscores the significance of controlling blood glycemic levels to reduce inflammation and mitigate

the likelihood of diabetes-related complications. It also implies that monitoring NLR in diabetic patients may provide further insight into their inflammatory status and overall progress.[23,24]

Conclusion

The positive correlation of neutrophil to lymphocyte ratio with insulin resistance and waist circumference in metabolic syndrome highlights the role of chronic inflammation in the disease progression.

Limitations and Recommendations: The study has limitations as patients were on medications for control of blood pressure and glucose levels which may affect the results. Moreover cross-sectional study does not provide causal relationship. Further longitudinal studies are needed to establish causality and explore potential therapeutic implications.

Conflict of Interest: *None*

Funding Disclosure: *None*

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Authors Contribution: All the authors contributed equally, in accordance with ICMJE guidelines and are accountable for the integrity of the study.

FA: Conception, design, data analysis, initial and final draft making, accountable.

HART: Analysis and interpretation, initial and final draft making, proof reading

NZ: Data acquisition, analysis, drafting and final revision, accountable

HSK: Revising the initial and final draft, data collection and data anallysis, accountable.