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Neutrophil-to-Lymphocyte Ratio and Insulin Resistance Relationship in Obese Individuals with Normal and Impaired Glucose Tolerance

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Abstract

Neutrophil-to-lymphocyte ratio (NLR) may be a predictor of glucose intolerance in obese individuals and may be useful in the early detection of glucose intolerance. In this study, we aimed to investigate the relationship between NLR and insulin resistance (IR) in obese individuals with normal and impaired glucose tolerance. Seventy-three obese patients and 27 healthy controls were included in this study. The participants' sociodemographic characteristics, anthropometric measurements (height, body weight, and waist circumference), fasting plasma glucose, oral glucose tolerance test (OGTT), insulin, HbA1c, total cholesterol, triglyceride, high-density lipoprotein (HDL), thyroid-stimulating hormone (TSH), complete blood count, and C-reactive protein (CRP) results were obtained from the files. Homeostasis Model Assessment Insulin Resistance (HOMA-IR) values were calculated. The mean age of the 100 patients was 36.4±10.5 years, and 59.0% were female. There was a statistically significant positive correlation between the HOMA-IR and the BMI (r = 0.457, p = 0.000), HbA1c (r = 0.359, p = 0.000), CRP (r = 0.444, p = 0.000), and waist circumference (r = 0.478, p = 0.000). There was no statistically significant difference between the obese and healthy control groups in terms of NLR. However, there was a significant difference in NLR, CRP, and neutrophil counts between the high HOMA-IR and normal HOMA-IR groups. In our study, neutrophil counts and CRP were determined to be higher among obese individuals than among healthy individuals. The NLR was increased significantly among patients with IR.

***Key words**: Obesity, Insulin resistance, Neutrophil-to-lymphocyte ratio.*

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Introduction

Obesity is an epidemic worldwide and increases the risk for many diseases, particularly insulin resistance (IR) and type 2 diabetes mellitus (T2DM). Obesity is considered a state of chronic and low-grade inflammation as well as increased oxidative stress (1). The relationship between chronic low-grade inflammation, IR, and other obesity-associated metabolic disturbances has become increasingly recognized (2).

Insulin resistance is common in patients with chronic inflammatory diseases characterized by unbalanced secretion of proinflammatory and anti-inflammatory cytokines. Measurement of IR provides an early and strong prediction of T2DM (3). The precise molecular effect leading to IR is not yet understood, but several studies have shown the relationship between systemic inflammation and IR (4, 5).

Recent studies have shown that combined indices derived from whole blood counts, such as neutrophil-to-lymphocyte ratio (NLR), are good indicators of systemic inflammation and immune status and are widely used in clinical diagnosis and prognosis evaluation. Generally, both acute and chronic inflammation cause elevated NLR through relative neutrophilia and lymphopenia. Neutrophil-to-lymphocyte ratio is a dynamic state and influenced by inflammatory cytokines and endocrine effects of the hypothalamic-pituitary axis (6, 7).

Previous studies indicate that an elevated NLR is associated with cardiovascular diseases (acute coronary syndrome outcomes, heart failure, and atrial fibrillation) (8-10). Also, NLR has been recently defined as a novel potential inflammation marker in many cancers and inflammatory diseases (11-13).

In a recent study, it was stated that NLR could be used as a marker for obese individuals with high IR, but the lack of measurement regarding other inflammatory markers such as C-reactive protein and demographic data (eg, waist circumference) stood out as important limitations in that study (14) .

Neutrophil-to-lymphocyte ratio may be a predictor of glucose intolerance in obese individuals and may be useful in the early detection of glucose intolerance. In this study, we aimed to evaluate the relationship between NLR and IR in obese individuals with normal and impaired glucose tolerance.

Materials and Methods

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Approval for the study was granted by the Gaziantep University Clinical Research Ethics Committee with decision number 2015/330. A total of 100 outpatients between the ages of 18-65 who applied to our Endocrinology and Metabolism Outpatient Clinics of the Department of Internal Medicine were included in this study from December 2014 to December 2015 and the files of the patients were scanned retrospectively. A body-mass index (BMI) of 18.5 to 25 kg/m^2 was considered normal, and a BMI of 30 kg/m^2 and higher was considered obese.

The participants were divided into 3 groups:

Group 1: Obese patients with normal glucose tolerance (NGT) (BMI $\geq$30 kg/m^2, n=43).

Group 2: Obese patients with impaired glucose tolerance (IGT) (BMI ≥30 kg/m^2, n=30).

Group 3: Healthy control group with impaired fasting glucose (normal BMI and NGT, n=27).

Major exclusion criteria were infectious conditions, malignancies, inflammatory rheumatic diseases, pregnancy, chronic kidney disease, acute and chronic liver disease. The participants' sociodemographic characteristics, anthropometric measurements (height, body weight, and waist circumference), fasting plasma glucose, OGTT, insulin, HbA1c, total cholesterol, triglyceride, HDL, TSH, complete blood count, and CRP results were obtained from the files.

Neutrophil-to-lymphocyte ratio was calculated as the simple ratio between the absolute neutrophil and lymphocyte count, which were both obtained from the same automated blood sample. Fasting insulin was measured by enzyme-linked immunosorbent assay, and IR was calculated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). Homeostatic Model Assessment for Insulin Resistance was calculated using the equation: HOMA-IR=Fasting insulin (μU/mL) x Fasting glucose (mg/dL) /405 and a HOMA-IR value of ≥2.5 was considered IR.

Statistical analysis

The normality of distribution of continuous variables was tested by the Kolmogorov Smirnov test. The independent samples t-test was used to compare two normally distributed independent groups, Mann–Whitney U-test to compare two non-normally distributed independent groups, and Kruskall Wallis test was used to compare three non-normally distributed independent groups. Relationships between categorical variables were tested with chi-square analysis, and relationships between numerical variables were tested with Spearman's rank correlation coefficient. SPSS for Windows version 22.0 package program was used for statistical analysis and $p<0.05$ was considered statistically significant.

Results

The mean age of the 100 patients was 36.4 ± 10.5 years, and 59.0% were female. Participants' socio-demographic characteristics, anthropometric measurement results, and laboratory analysis results are shown in Table 1. CRP and neutrophil counts were significantly higher in the IGT and NGT obese groups compared to the healthy control group ($p = <0.001$ and $p = 0.007$, respectively). NLR was found to be higher in individuals with high HOMA-IR compared to those with normal HOMA-IR ($p = 0.050$) (Table 2). There was a statistically significant positive correlation between the HOMA-IR and the BMI ($r = 0.457$, $p = 0.000$), HbA1c ($r = 0.359$, $p = 0.000$), CRP ($r = 0.444$, $p = 0.000$), and waist circumference ($r = 0.478$, $p = 0.000$) (Table 3).

Table 1: Participants' socio-demographic characteristics, anthropometric measurement results, and laboratory analysis results.

	IGT obese (n=30)	NGT obese (n=43)	Healthy control (n=27)	*p*	Total (n=100)
Gender					
Female	17 (56.7%)	26 (60.5%)	16 (59.3%)	0.948	59 (59.0%)
Male	13 (43.3%)	17 (39.5%)	11 (40.7%)		41 (41.0%)
Age(years) [#]	41.5±9.3*	34.3±11.8	34.1±7.3	0.005*	36.4±10.5
BMI (kg/m²)[#]	37.3±6.5*	34.4±4.4*	24.0±2.7*	<0.001*	32.4±7.1
Waist circumference (cm) [#]	121.1±11.9*	114.7±15.4*	84.9±12.3*	<0.001*	108.5±20.0
Insulin (mU/ml) [†]	13.6	9.9	6.0*	<0.001*	9.6
HbA1c (%)[†]	6.0*	5.5	5.4	0.001*	5.6
HOMA-IR[†]	3.4	2.2	1.3*	<0.001*	2.2
Total cholesterol (mg/dl) [†]	209	197	200	0.662	199
Triglyceride (mg/dl) [†]	157	151	117	0.082	146
HDL (mg/dl) [†]	49	45*	53*	0.007*	48
TSH (uIU/mL) [†]	2.3	2.5	1.5*	<0.001*	2.1
CRP (mg/dl) [†]	4.6	4.1	1.2*	<0.001*	2.9
Neutrophil (10^{3}/µL) [†]	4745*	4310	3710*	0.007*	4245
Lymphocyte (10^{3}/µL) [†]	2645	2500	2200	0.076	2495
NLR[†]	1.78	1.53	1.65	0.880	1.63

*$p \leq 0.05$. [#]Data are presented as mean±SD; [†]Data are presented as median; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; BMI, body mass index; HOMA-IR, the homeostasis model assessment-estimated insulin resistance; CRP, C-reactive protein**;** NLR, neutrophil-to-lymphocyte ratio.

Table 2: Comparison of the participants according to HOMA-IR values.

	HOMA-IR <2.5 (n=56)	HOMA-IR ≥2.5 (n=44)	*p*	Total (n=100)
Gender				
Female	36 (64.3%)	23 (52.3%)	0.306	59 (59.0%)
Male	20 (35.7%)	21 (47.7%)		41 (41.0%)
Age(years) [#]	34.3±10.2	39.1±10.3	0.024*	36.4±10.5
BMI (kg/m²)[#]	30.0±6.3	35.5±7.0	<0.001*	32.4±7.1
Waist circumference (cm) [#]	100.1±19.0	118.2±17.0	<0.001*	108.5±20.0
Insulin (mU/ml) [†]	6.7	16.9	<0.001*	9.6
HbA1c (%)[†]	5.4	5.8	<0.001*	5.6
Total cholesterol (mg/dl) [†]	196	209	0.158	199
Triglyceride (mg/dl) [†]	124	174	0.002*	146
HDL (mg/dl) [†]	50	45	0.045*	48
TSH (uIU/mL) [†]	1.9	2.3	<0.001*	2.1
CRP (mg/dl) [†]	1.9	4.5	<0.001*	2.9
Neutrophil (10^{3}/µL) [†]	3930	4765	0.005*	4245
Lymphocyte (10^{3}/µL) [†]	2505	2495	0.721	2495
NLR[†]	1.51	1.84	0.050*	1.63

*p≤0.05. [#]Data are presented as mean±SD; [†]Data are presented as median; BMI, body mass index; HOMA-IR, the homeostasis model assessment-estimated insulin resistance; CRP, C-reactive protein**;** NLR, neutrophil-to-lymphocyte ratio.

Table 3: Correlation analysis results between categorical variables.

		Age	BMI	Waist circumference	Insulin	HbA1c	CRP	NLR	HOMA-IR
Age	r		0.302	0.401	0.102	0.364	0.082	-0.064	0.148
	p		0.002*	0.000*	0.313	0.000*	0.415	0.529	0.141
BMI	r	0.302		0.847	0.420	0.339	0.588	-0.012	0.457
	p	0.002*		0.000*	0.000*	0.001*	0.000*	0.903	0.000*
Waist	r	0.401	0.847		0.459	0.279	0.519	0.007	0.478
circumference	*p*	0.000*	0.000*		0.000*	0.005*	0.000*	0.944	0.000*
Insulin	r	0.102	0.420	0.459		0.322	0.394	0.133	0.980
	p	0.313	0.000*	0.000*		0.001*	0.000*	0.188	0.000
HbA1c	r	0.364	0.339	0.279	0.322		0.428	-0.037	0.359
	p	0.000*	0.001*	0.005*	0.001*		0.000*	0.718	0.000
CRP	r	0.082	0.588	0.519	0.394	0.428		0.148	0.444
	p	0.415	0.000*	0.000*	0.000*	0.000*		0.142	0.000
NLR	r	-0.064	-0.012	0.007	0.133	-0.037	0.148		0.126
	p	0.529	0.903	0.944	0.188	0.718	0.142		0.212
HOMA-IR	r	0.148	0.457	0.478	0.980	0.359	0.444	0.126	
	p	0.141	0.000*	0.000*	0.000*	0.000*	0.000*	0.212	

r: Spearman rank correlation coefficient. *Significant at 0.01 level. BMI, body mass index; CRP, C-reactive protein (mg/dl); NLR, neutrophil-to-lymphocyte ratio; HOMA-IR, the homeostasis model assessment-estimated insulin resistance.

Discussion

Our study has shown that IR, BMI, CRP, neutrophil, and waist circumference were significantly higher in the obese patients with IGT and NGT compared to the healthy control group. There was no statistically significant difference for the NLR between groups. However, we observed that both NLR and neutrophil count increased as the IR level increased.

Experimental studies have demonstrated a link between chronic inflammation and IR through mechanisms that include obesity and atherosclerosis (15)(16). Obesity is also associated with inflammation. A previous study revealed that obesity, defined by BMI and waist circumference, was associated with inflammation (17).

Studies evaluating the relationship between NLR and obesity have shown that other markers such as CRP are more closely associated with obesity, and NLR tends to increase in obese patients (18)(19)(20). Previous studies illustrated that NLR could be a potential surrogate marker of systemic inflammation with its ability to predict CRP levels (21)(22). However, some studies opposed these observations. A study conducted in Turkey has reported that NLR was similar in obese and non-obese individuals (14). Also in a study, NLR was not found to be a good indicator of inflammation, while hs-CRP and leukocytes were more useful biomarkers to indicate inflammation in non-diabetic patients with obesity (23).

In one study, NLR was found to be higher in individuals with IGT, newly diagnosed with diabetes by OGTT, and previously diagnosed with diabetes compared to individuals with NGT (24). Additionally, a study showed that NLR is a risk factor for IR with DM (25).

Imtiaz et al. demonstrated that systemic inflammation measured by NLR is closely associated with prevalent chronic conditions such as hypertension and diabetes (13). Another study has demonstrated the association of NLR with glucose intolerance and IR severity (26).

According to our results, we observed that HOMA-IR and HbA1c values were higher among the obese patient group with IGT than the obese patient group with NGT, while the NLR was similar between the two groups.

The present study had several limitations. This preliminary study involved a retrospective analysis of a small population from a single institution. Despite these limitations, this study has some strengths. We included participants without comorbidities that could affect inflammatory parameters, thereby ensuring more homogeneous groups of participants. In addition, combining anthropometric measurements and laboratory measurements was one of the strengths of our study.

In conclusion, neutrophil counts and CRP were determined to be higher among obese individuals than among healthy individuals in our study. Also, NLR, neutrophil counts, and CRP were found to be significantly higher in individuals with IR compared to individuals without IR.

Studies with prospective designs and multiple NLR measurements may provide more robust evidence to demonstrate the role of NLR as a marker of subclinical inflammation and a predictor of prediabetes risk.

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