THE INJECTOR

DOI: 10.5281/zenodo.8072274
The Injector 2023;2(2):77-82

Original Article

Do insulin resistance and inflammation parameters change according to the blood types in non-obese healthy individuals?

Orkun Sarıçam

Ankara Pursaklar State Hospital, Department of Internal Medicine, Ankara, Turkey

Abstract

Objective: Insulin resistance (IR) is defined as a decrease in insulin sensitivity in tissues targeting insulin and is a risk factor for many diseases. In this study, we aimed to elucidate the relationship of insulin resistance, inflammation parameters and blood types in non-obese healthy individuals.

Methods: A total of 275 volunteers without any chronic disease who applied for check-up were included in the study. Demographic characteristics, body mass index, biochemical parameters, hemogram and blood types of the patients were recorded and compared between groups.

Results: Of the 17.5% (n=48) individuals who had insulin resistance and those with BMI <25 were included in the study. C-reactive protein (CRP), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and systemic immune-inflammatory index (SII) values were significantly higher in those with IR than those without IR ($p<0.05$). In those with IR, the rate of those with AB blood type was found to be significantly higher than the rate of those with blood type 0 ($p=0.017$).

Conclusion: We found that subclinical chronic inflammation indicators such as NLR, PLR, SII and CRP were significantly higher in non-obese and healthy individuals with IR than those without IR. Curative treatments to be initiated in the early period in individuals with IR may provide additional therapeutic benefits beyond lowering glucose, preventing metabolic diseases.

Keywords: ABO blood types, insulin resistance, inflammation, obesity.

Address for correspondence: Orkun Sarıçam, Ankara Pursaklar State Hospital, Department of Internal Medicine, Ankara, Turkey.
Phone: +90 312 509 70 00 **E-mail:** orkunsar@hotmail.com **ORCID:** 0000-0001-5820-0951
Received: 15 November 2022 **Revised:** 9 February 2023 **Accepted:** 5 June 2023 **Published:** 23 June 2023

INTRODUCTION

Insulin resistance (IR) is defined as decreased insulin sensitivity in tissues that target insulin, such as adipose tissue, muscle, and liver, and is a risk factor for many diseases, such as type II diabetes (T2D), cardiovascular disease, non-alcoholic fatty liver disease (NAFLD), and metabolic syndrome (1, 2). Although several mechanisms play a role in the development of IR, the mechanisms by which inflammation increases insulin resistance have recently come to the fore (3).

Paracrine and/or endocrine factors that induce insulin resistance in target cells such as adipocytes or hepatocytes are thought to play a role in inflammatory insulin resistance (3). Cytokines that are most commonly involved in insulin resistance include TNF-α and interleukin–1β (IL–1β). Additionally, cytokine receptor activation in insulin target cells is thought to activate signaling pathways that directly or indirectly impair insulin action (4).

T2D is characterized by elevated blood glucose levels and insulin resistance due to impaired insulin signaling in insulin-targeted tissues, and is one of the major causes of obesity (5). Studies have shown that insulin resistance can develop in individuals with normal body weight, and if not treated, cardiovascular disease and T2D can develop (6, 7).

Although there are many studies on insulin resistance in obese patients, the data are limited on the pathophysiology of insulin resistance in non-obese individuals (8). In this study, we aimed to elucidate the relationship between insulin resistance, inflammation parameters and blood types in non-obese healthy individuals.

MATERIALS AND METHODS

A total of 275 healthy volunteers without any disease who applied to the internal medicine outpatient clinic for check-up were included in the study. The study was approved by Health Sciences University Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (2022-06/139/26). All procedures were applied in accordance with the principles of the Declaration of Helsinki.

Individuals with a history of chronic disease (cardiac diseases, diabetes, hypertension, lung diseases, chronic kidney failure, thyroid abnormalities, liver or hematologic disorders), malignities, immunodeficiency, thalassemia, history of acute or chronic inflammatory disease, pregnancy, infection and medication in the last 1 month were excluded. Non-obese (BMI<25 kg/m^2) individuals were included in the study and were classified as those with and without insulin resistance. Those who were obese and overweight (BMI>25 kg/m^2) and those with the above mentioned chronic diseases were excluded from the study.

Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following equation: HOMA-IR= Fasting Glucose (mg/dL) X Fasting Insulin (μIU/mL)/405. Individuals with HOMA scores of ≥2.7 were considered to have IR (9). Demographic characteristics, biochemical parameters, hemogram, C-reactive protein (CRP), insulin and blood types were recorded. Systemic immune-inflammation index (SII)= neutrophil count X platelet count/lymphocyte count formula, NLR= neutrophil count divided by lymphocyte count; PLR=platelet number divided by lymphocyte number, monocyte to high density lipoprotein ratio (MHR) was obtained by dividing monocyte number by HDL number (10, 11).

Statistical analysis

The data were analyzed via IBM SPSS Statistics 28 package program. While evaluating the study data, frequencies (number, percentage) were given for categorical variables, and descriptive statistics (mean, standard deviation) were given for numerical variables. The normality assumptions of the numerical variables were examined with the Kolmogorov Smirnov normality test and it was seen that the variables were not normally distributed. For this reason, non-parametric statistical methods were used in the study. The differences between the two independent types were checked with the Mann Whitney U Test, and the relationships between the two independent categorical variables were checked with the Chi-Square analysis. A p value of 0.05 has been accepted as statistically significant.

RESULTS

The mean age of the patients included in the study was 31.81±10.35 years and 69.1% (n=190) were female. Insulin resistance was present in 17.5% (n=48) of the patients and the mean body mass index was 22.39± 2.33 kg/m^2. The blood type of 43.6% of the patients was A, 25.1% was 0, 18.2% was B and 13.1% was AB (Table 1).

When inflammation parameters were compared between the groups with and without insulin resistance, statistically significant differences were found in the values of white blood cells (WBC), neutrophils, platelets, NLR, PLR, SII and CRP ($p<0.05$). Neutrophil, platelet, NLR, PLR and SII values were significantly higher in those with insulin resistance than those without insulin resistance ($p<0.001$). WBC and CRP values of patients with insulin resistance were found to be significantly higher than those without insulin resistance ($p=0.002$, $p=0.027$) (Table 2).

As a result of chi-square analysis, a statistically significant relationship has been achieved between patients with insulin resistance and blood types ($p<0.05$). The rate of those with blood type AB had significantly higher insulin resistance was compared to those with blood type 0 ($p=0.017$) (Table 3).

Table 1. Demographic characteristics of the individuals

	(n=275)	n (%)
Gender		
Male		85 (30.9)
Female		190 (69.1)
Insulin resistance		
Yes		48 (17.5)
No		227 (82.5)
Blood types		
0		69 (25.1)
A		120 (43.6)
B		50 (18.2)
AB		36 (13.1)
		Mean±SD
Age (year)		31.81±10.35
Glucose (mg/dl)		91.85±8.31
Insulin (mU/l)		7.42±7.96
BMI (kg/m^2)		22.39±2.33

Abbreviations: BMI: Body Mass Index

DISCUSSION

Although obesity is recognized as an important cause of T2D, 50% of patients with T2D in Europe and more than 60% in Asia are not obese according to WHO criteria (BMI<30 kg/m^2) (12). These results led researchers to investigate the causes of T2D and insulin resistance in non-obese patients. In previous literature, inflammation and environmental factors in which inflammatory markers such as IL-6, Th17 and IFN-γ play a role in the etiology in non-obese patients have come to the fore more than visceral fat deposition (13,14). The mean age of the patients in our study was 31.81±10.35 years, the mean BMI was 22.39±2.33 kg/m^2, and insulin resistance has been observed in 17.5% (n=48) of the patients.

Previous studies have found associations with elevated NLR, PLR and SII levels in conditions with chronic inflammation such as diabetes mellitus, obesity, atherosclerotic events, various cancers types and metabolic syndrome (15–17). The fact that insulin resistance is an important risk factor for T2D, hypertension, metabolic syndrome and cardiovascular diseases suggested that insulin resistance may be associated with inflammatory parameters such as NLR, PLR and SII in the blood (18). However, it was previously shown that insulin mediates the regulation of some functions such as stimulating the chemokinesis of neutrophils and has an increasing effect on proliferation and cytokine production on lymphocytes (19,20). In our study, we found that the NLR, PLR and

Table 2. Biochemical results according to the insulin resistance

	Insulin resistance		Chi-Square	P
	Yes n (%)	No n (%)		
Gender				
Male	18 (21.2)	67 (78.8)	1.183	0.277
Female	30 (15.8)	160 (84.2)		
	Value	**Value**	**Z**	**P**
Age (year)	31.56±9.71	31.86±10.50	-0.088	0.930
Glucose (mg/dl)	97.00±9.26	90.77±7.69	-4.202	**<0.001***
Insulin (mU/l)	20.35±11.37	4.68±2.64	-10.843	**<0.001***
WBC ($\times 10^3$ µl)	7.67±1.22	7.31±5.70	-3.156	**0.002***
Neu ($\times 10^3$ µl)	5.60±1.83	3.95±1.11	-6.170	**<0.001***
Lym ($\times 10^3$ µl)	2.21±0.56	2.47 (0.9-30.3)	-0.688	0.492
Plt ($\times 10^3$ µl)	339.2±80.2	265±57.7	-5.866	**<0.001***
Mon ($\times 10^3$ µl)	0.40±0.11	0.53 (0.1-7.9)	-0.153	0.879
Ferritin (mg/l)	41.7 (3.6-147.6)	38.8 (0.04-256)	-1.198	0.231
NLR	2.76±1.31	1.87±0.70	-5.078	**<0.001***
PLR	165.6±66.0	126.4±43.7	-4.181	**<0.001***
SII	934.8±473.9	497.3±230.1	-6.550	**<0.001***
CRP (mg/l)	0.48 (0-6.5)	0.39 (0-10)	-2.208	**0.027***
BMI (kg/m^2)	22.82±2.21	22.30±2.35	-1.388	0.165

Abbreviations: Z: Mann Whitney U, *: p<0.05 WBC: White Blood Cell, Neu: Neutrophils, Lym: Lymphocytes, Plt: Platelets, Mon: Monocytes, NLR: Neutrophil/Lymphocyte Ratio, PLR: Platelet/Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, CRP: C-Reactive Protein, BMI: Body Mass Index

Table 3. Examining of the relationship between insulin resistance and blood types

	Insulin resistance		Chi-Square	p
	Yes n (%)	No n (%)		
Blood types				
0	6 (8.7$_a$)	63 (91.3$_a$)		
A	20 (16.7$_{a,b}$)	100 (83.3$_{a,b}$)	10.251	**0.017***
B	10 (20.0$_{a,b}$)	40 (80.0$_{a,b}$)		
AB	12 (33.3$_b$)	24 (66.7$_b$)		

Abbreviations: *: p<0.05, The 'a' and 'b' indices were used to show the difference.

SII values of non-obese patients with IR who did not have any chronic disease were significantly higher than those without IR. Similarly, Lou et al. elaborated that high NLR values could be a reliable marker of IR in newly diagnosed diabetic patients (21).

CRP is a chronic subclinical indicator of infection, which has been previously shown to be associated with insulin resistance and is a risk factor for cardiovascular diseases and T2D (22). Yudgin et al. showed that CRP values in healthy individuals were associated with insulin resistance and endothelial dysfunction, independent of anthropometric measurements of obesity (23). In another multicenter study conducted with non-diabetic populations, chronic subclinical inflammation displayed by inflammatory markers such as CRP and WBC was found to be directly related to IR (24). Similarly, in our study, we found that neutrophil, platelet, WBC and CRP values of those with IR were significantly higher than those without IR in non-obese healthy individuals. We thought that these results supported the existence of subclinical infection in non-obese and healthy individuals with IR.

It is thought that blood type antigens are among the hereditary determinants that have an important place in understanding the susceptibility to many diseases (25). Studies have shown that ABO and Rh blood type antigens were associated with coronary heart disease, various cancers, diabetes, and especially T2D (26). Some investigators stated that B blood type was associated with a higher risk of developing T2D while 0 blood type was associated with a lower risk (25,27). In our study, we found that the rate of T2D in patients with IR was significantly higher in AB blood type than those with 0 blood type. Zhang et al., compared 0 blood type with other types and stated that cardiovascular disease risk was found to be significantly higher in blood types other than 0 (28). We thought that our results supported the low-risk results for 0 blood type in the development of metabolic diseases as shown in other research.

Limitations:

Since IR was investigated in non-obese healthy individuals in this study, the limited number of patients in the IR group constituted the limitation of the study. More detailed evaluations with larger patient groups are required to obtain definitive results.

CONCLUSION

We found that subclinical chronic inflammation indicators such as NLR, PLR, SII and CRP were significantly higher in non-obese and healthy individuals with IR than those without IR. Curative treatments to be initiated in the early period in individuals with IR may provide additional therapeutic benefits beyond lowering glucose, preventing metabolic diseases.

Conflicts of interest: The author declares no conflict of interest.
Financial support and sponsorship: None.
Ethical approval and consent to participate: The study was approved by Health Sciences University Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (2022-06/139/26). All procedures were applied in accordance with the principles of the Declaration of Helsinki.
Author contributions: Design of the study; OS -Supervision; OS -Data collection &/or processing; OS -Performed data analysis; OS -Literature search; OS -Written by; OS-Critical review; OS.

References

1. Czech MP. Insulin action and resistance in obesity and type 2 diabetes. Nature Medicine. 2017;23(7):804–14.
2. Patel TP, Rawal K, Bagchi AK, Akolkar G, Bernardes N, Silva Dias D, et al. Insulin resistance: an additional risk factor in the pathogenesis of cardiovascular disease in type 2 diabetes. Heart Failure Reviews. 2016;21(1):11–23.
3. Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. Annu Rev Physiol. 2010;72:219–46.
4. Petersen MC, Shulman GI. Mechanisms of Insulin Action and Insulin Resistance. Physiol Rev. 2018;98(4):2133–223.
5. Lee SH, Park SY, Choi CS. Insulin Resistance: From Mechanisms to Therapeutic Strategies. Diabetes Metab J. 2022;46(1):15–37.
6. Mc Keown RE. The Epidemiologic Transition: Changing Patterns of Mortality and Population Dynamics. Am. J. Lifestyle Med. 2009;3:19S–26S.
7. Misra A, Gopalan H, Jayawardena R, Hills AP, Soares M, Reza-Albarran AA, et al. Diabetes in developing countries. J. Diabetes. 2019;11:522–39.
8. Tan HC, Yew TW, Chacko S, Tai ES, Kovalik JP, Ching J, et al. Comprehensive assessment of insulin resistance in non-obese Asian Indian and Chinese men. 2018;9(6): 1296-303.
9. Topsakal S, Yerlikaya E, Akin F, Kaptanoglu B, Erürker T. Relation with HOMA-IR and thyroid hormones in obese Turkish women with metabolic syndrome. Eat Weight Disord 2012;17(1): e57-61.
10. He K, Si L, Pan X, Sun L, Wang Y, Lu J, et al. Preoperative Systemic Immune–Inflammation Index (SII) as a Superior Predictor of Long-Term Survival Outcome in Patients With Stage I–II Gastric Cancer After Radical Surgery Front Oncol. 2022;12:829689.
11. Platini H, Ferdinand E, Kohar K, Prayogo SA, Amirah S, Komariah M, et al. Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio as Prognostic Markers for Advanced Non-Small-Cell Lung Cancer Treated with Immunotherapy: A Systematic Review and Meta-Analysis. Medicina (Kaunas) 2022;58(8):1069.
12. Vaag A, Lund SS. Non-obese patients with type 2 diabetes and prediabetic subjects: distinct phenotypes requiring special diabetes treatment and (or) prevention? Appl Physiol Nutr Metab. 2007;32:912–20.
13. Chuang HC, Tan TH. MAP4K4 and IL-6+ Th17 cells play important roles in non-obese type 2 diabetes. J Biomed Sci. 2017;24:4.

14. Jagannathan-Bogdan M, Mc Donnell ME, Shin H, Rehman Q, Hasturk H, Apovian CM, et al. Elevated proinflammatory cytokine production by a skewed T cell compartment requires monocytes and promotes inflammation in type 2 diabetes. J Immunol. 2011;186:1162–72

15. Wang JR, Chen Z, Yang K, Yang HJ, Tao WY, Li YP, et al. Association between neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and diabetic retinopathy among diabetic patients without a related family history. Diabetol Metab Syndr. 2020;12:55.

16. Liu J, Ao W, Zhou J, Luo P, Wang Q, Xiang D. The correlation between PLR-NLR and prognosis in acute myocardial infarction. Am J Transl Res. 2021;13(5):4892–99.

17. Liu J, Li S, Zhang S, Liu Y, Ma L, Zhu J, et al. Systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio can predict clinical outcomes in patients with metastatic non-small-cell lung cancer treated with nivolumab. J Clin Lab Anal. 2019;33(8): e22964.

18. Lee SH, Park SY, Choi CS. Insulin Resistance: From Mechanisms to Therapeutic Strategies. Diabetes Metab J. 2022;46(1):15–37.

19. Cruz-Pineda WD, Parra-Rojas I, Rodríguez-Ruíz HA, Illades-Aguiar B, Matia-García I, Garibay-Cerdenares OL. The regulatory role of insulin in energy metabolism and leukocyte functions. J Leukoc Biol. 2022;111(1):197–208.

20. Tsai S, Clemente-Casares X, Zhou AC, Lei H, Ahn JJ, Chan YT, et al. Insulin receptor-mediated stimulation boosts T cell immunity during inflammation and infection. Cell Metab. 2018;28(6):922-34.

21. 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.

22. Lorenzo C, Festa A, Hanley AJ, Rewers MJ, Escalante A, Haffner SM. Novel Protein Glycan–Derived Markers of Systemic Inflammation and C-Reactive Protein in Relation to Glycemia, Insulin Resistance, and Insulin Secretion. Diabetes Care. 2017;40(3):375–82.

23. Yudkin JS, Stehouwer CDA, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction. Arterioscler Thromb Vasc Biol.1999; 19:972–8.

24. Festa A , D'Agostino R Jr, Howard G, Mykkänen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). 2000;102(1):42-7.

25. Getawa S, Bayleyegn B, Aynalem M, Worku YB, Adane T. Relationships of ABO and Rhesus blood groups with type 2 diabetes mellitus: a systematic review and meta-analysis. J Int Med Res. 2022;50(10):03000605221129547.

26. Abegaz SB. Human ABO Blood Groups and Their Associations with Different Diseases. Biomed Res Int. 2021;2021:6629060.

27. Legese B, Abebe M, Fasil A. Association of ABO and Rh Blood Group Phenotypes with Type 2 Diabetes Mellitus at Felege Hiwot Comprehensive Referral Hospital Bahir Dar, Northwest Ethiopia. Int J Chronic Dis. 2020;2020:2535843.

28. Zhang Y, Li S, Zhu CG, Guo YL, Wu NO, Xu RX, et al. Risk Factors, Coronary Severity, Outcome and ABO Blood Group. Medicine (Baltimore). 2015;94(43):e1708.