

The Value of Neutrophil Lymphocyte Ratio in Predicting the Degree of Insulin Resistance and β Cell Dysfunction in Type 2 Diabetic Patients

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Abstract: Objective: Insulin resistance and progressive pancreatic β -cell failure are key factors in the development of type 2 diabetes. The aim of the present study was to define the relationship between Neutrophil Lymphocyte Ratio (NLR) and the degree of insulin resistance and β cell dysfunction in Type 2 Diabetes Mellitus. Methods: This study was carried out on seventy diabetic patient attended the outpatient clinic of the diabetes and metabolism unit in Alexandria Main University Hospital (AMUH) and thirty t healthy subjects with matched age, sex and socioeconomic status as a control group. Subjects were interviewed in order to collect data using predesigned questionnaire, anthropometric measures were measured, blood samples were collected from each subject for chemical analysis. Results: NLR was higher in diabetic subjects than non-diabetic one. NLR showed significant positive correlation with HOMA-IR and no significant negative correlation with HOMA- β . Conclusion: the relation between inflammation and adipose tissue is extremely complex in diabetic patients. However, simple calculation of NLR and measurement of waist circumference can reveal inflammation in the diabetic population.

Keywords: Insulin Resistance Syndrome, Beta Cell Dysfunction, Neutrophil Lymphocyte Ratio (NLR)

1. Introduction

Type 2 diabetes mellitus (T2DM) is the most common form of diabetes, constituting 90 % of the estimated 382 million diabetes cases worldwide in 2013.⁽¹⁾ It's becoming a serious global health problem, especially in countries of low and middle income, where the prevalence is increasing the most, and where the age of debut is relatively low. The WHO estimates that diabetes will be the 7th most common cause of death by 2030.⁽²⁾ Development of T2DM requires two major elements: insulin resistance, leading to ineffective insulin action, and β -cell dysfunction, leading to inappropriate insulin secretion.⁽³⁾

Insulin resistance and progressive pancreatic β -cell failure are key factors in the development of T2DM. Several studies

have supported the hypothesis that chronic subclinical inflammation may be associated with insulin resistance and precede the development of clinically overt T2DM.^(4,5) Risk factors for developing diabetes, such as obesity, physical inactivity, smoking, dietary habits, psychological stress and infections, are considered to be activators of the innate immune system that induce a state of chronic low-grade inflammation. Proinflammatory cytokines enhance insulin resistance through molecular pathways that involve activation of Jun kinase (JNK), activation of I κ B kinase- β /nuclear factor κ B and down regulation of PPAR γ expression.^(5,6)

Measures designed to reduce the inflammatory process could be of benefit in reducing the risk of both diabetes and

cardiovascular disease.⁽⁷⁾ Some have associated the consumption of various dietary components with sensitive inflammatory markers, implying that the type and quality of diet may have a significant impact on the inflammatory process.⁽⁸⁾ The exact association between physical activity and inflammation is not known, however.⁽⁹⁾

Obesity results in low grade chronic inflammation, by some authors termed “metaflammation”. Overweight and obese adipose tissue secretes inflammatory markers and cytokines/adipokines which have been closely linked to insulin resistance. Inflammation increases the infiltration of immune cells, mainly macrophages, but also lymphocytes and mast cells, into the adipose tissue, in turn contributing to the increasing secretion of cytokines.⁽¹⁰⁾

The aim of the present study was to: To investigate the possible value of NLR as a new simple reliable marker of systemic inflammation in predicting the degree of insulin resistance and β cell dysfunction in T2DM.

2. Patients and Methods

2.1. Patients

This study was carried out on seventy diabetic patient attended the outpatient clinic of the diabetes and metabolism unit of AMUH and thirty healthy subjects with matched age, sex and socioeconomic status as a control group.

2.2. Methods

Subjects were interviewed in order to collect data using predesigned questionnaire, anthropometric measures were calculated, the subjects were clinically evaluated. Blood samples were collected from participants and analyzed for total, differential WBCs, fasting blood sugar, fasting serum insulin, C-reactive protein, erythrocyte sedimentation rate, and lipid profile. Insulin resistance by Homeostatic Model Assessment (HOMA-IR), β cell function by Homeostatic Model Assessment (HOMA- β) and NLR were calculated as follow:

$HOMA-IR = (\text{fasting glucose in mg/dl} \times \text{fasting insulin in mU/l}) / 405$ and $HOMA- \beta (\%) = (\text{fasting insulin in mU/l} \times 360) / (\text{fasting glucose in mg/dl} - 63)$.⁽¹¹⁾ NLR calculated using the differential count by dividing the absolute neutrophil count by the absolute lymphocyte count.⁽¹²⁾

3. Results

- NLR was higher among diabetic patients than among subjects in the control group with no statistical differences between them (table 1& figure 1).
- Among cases, significant positive correlation was found between NLR with BMI, HbA1c, and HOMA-IR while significant negative correlation was found between NLR and HDL. Among subjects in the control group, significant negative correlation was found between LDL and NLR. Otherwise, the correlation between NLR and other different parameters showed no statistical

significance in both groups. (Figure 2).

- Among cases, significant positive correlation was found between BMI of and HOMA-IR while non-significant negative correlation was found between BMI and HOMA- β . (Table 2).
- After adjustment of age, smoking, waist hip ratio, fasting blood sugar, fasting serum insulin, total cholesterol, serum TG, HDL and LDL, there were significant positive association between NLR and duration of DM, BMI, and HbA1c. Significant negative association was found between NLR and both serum HDL. (Table 2).

Table 1. Comparison between the two studied groups according to mean NLR level.

Variables	Cases(n = 70)	Control(n = 30)	Test of sig.	p
NLR				
Min. – Max.	0.26 – 2.87	0.01 – 2.95		
Mean \pm SD.	1.99 \pm 0.53	1.82 \pm 0.64	t= 1.406	0.163
Median	2.04	1.93		

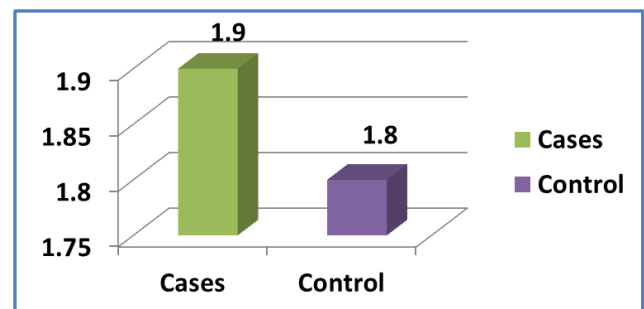


Figure 1. Comparison between the two studied groups according to the mean NLR level.

Table 2. Multiple regression analysis of NLR among cases.

Variable	β	P-value
Duration of DM	0.441	<0.001*
BMI	0.389	<0.001*
HDL	-0.215	0.002*
HbA1c	0.585	<0.001*
Model significance	<0.001*	
Adjusted model R ²	0.734	

*P<0.05.

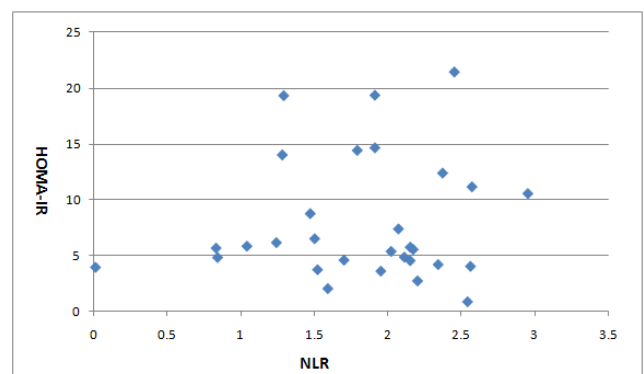


Figure 2. Correlation between HOMA-IR and NLR among cases.

4. Discussion

In the present study, the mean NLR was higher among diabetic cases than the control group (1.99 ± 0.53 vs. 1.82 ± 0.64 respectively). A cross-sectional study carried out in Turkey and included 200 type 2 diabetic patients concluded that calculation of NLR can simply predict inflammation in diabetic population.⁽¹³⁾ Sahin et al. (2013) found the mean NLR level among diabetic patients included in their studies was higher than that detected in the present study (2.87 ± 1.3).⁽¹⁴⁾ This difference among results between the studies might be attributed to Atrial Fibrillation (AF) that noticed among diabetic subjects in Sahin et al. study compared to Normal Sinus Rhythm (NSR) in the current study.

In the current study, results revealed positive associations of blood glucose and insulin levels and HbA1c with NLR. Pitsavos et al (2007) also found an association between NLR as a marker of low-grade inflammation and FBS and HbA1c as indices of glycemic control indices.⁽¹⁵⁾ Pearson correlation analysis in a cross sectional study carried out by shiny et al. (2014) showed a significant positive correlation of NLR with glycated hemoglobin ($r=0.411$), and fasting plasma glucose ($r=0.378$).⁽¹⁶⁾ Sefil et al (2014) noticed raised NLR associated among diabetic patients included in the study. They further related NLR with blood glucose regulation.

Significant relationship between NLR and BMI was also noticed in the current study. This underlines the important role of adipose tissue in the activation and development of low-grade inflammation. Excess of adipose tissue, as a source of pro-inflammatory cytokines, may increase WBC count in blood. The pro-inflammatory state induced by hyperglycemia and obesity, and developing in vessels, directly influences metabolism of endothelial cells and development of microangiopathy.⁽¹⁷⁾ The best way to reduce the level of low-grade inflammation is good glycemic control in diabetes patients and maintenance of proper body weight in all patients.

HDLs are a class of lipoproteins that promote the efflux of excess cholesterol from cells and return it to the liver for secretion into the bile. Previous studies consider HDLs to be part of the innate immune system, functioning to inhibit inflammation in the absence of an acute phase response.^(15,18) In a previous work, an inverse association of inflammatory markers with HDL levels was found, suggesting that increased levels of HDL may lead to decreased low-grade inflammation in healthy individuals.⁽¹⁹⁾ In the present study, diabetic patients had significantly lower HDL cholesterol levels than non-diabetic participants. This was strengthened by findings of Pitsavos et al.⁽¹⁵⁾

NLR was not correlated with β -dysfunction (HOMA- β) while NLR was positively correlated with insulin resistant (HOMA-IR). In multiple regression analysis, neither HOMA- β nor HOMA-IR is significantly associated with NLR. These findings were exactly agreed with those of Lee et al. (2014).⁽²⁰⁾ They carried out their study upon 656 nondiabetic participants in the cohort and they stated that

association of NLR with insulin resistance was confounded by obesity. NLR showed positive correlation with HOMA-IR, insulin, glucose, and HDL cholesterol levels in Turkmen et al. (2013) study which carried out upon 29 subjects with Autosomal Dominant Polycystic Kidney Disease (ADPKD).⁽²¹⁾

5. Conclusion

In summary, the relation between inflammation and adipose tissue is extremely complex in diabetic patients. However, simple calculation of NLR and measurement of waist circumference can reveal inflammation in the diabetic population.

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