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Original Article

Usefulness of the neutrophil-to-lymphocyte ratio to prediction of type 2 diabetes mellitus in morbid obesity

H. Yilmaz [a,*], B. Ucan [b], M. Sayki [b], I. Unsal [b], M. Sahin [b], M. Ozbek [b], T. Delibasi [b]

[a] Turgut Ozal University School of Medicine, Department of Internal Medicine, Turkey
[b] Dışkapı Yıldırım Beyazıt Education and Researching Hospital, Department of Endocrinology and Metabolism, Turkey

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ABSTRACT

Background: There is growing consensus in the literature that inflammation plays a central role in the pathophysiology of obesity and type 2 diabetes mellitus (T2DM) and cardiovascular complications. Neutrophil-to-lymphocyte ratio (NLR) provides a simple method for assessment of inflammatory status and it is a new, inexpensive marker. The aim of the present study was to investigate the predictive value of preprocedural (before the OGTT) NLR on development of type 2 diabetes (T2DM) in morbid obesity patients (MOP).

Methods: 306 MOP (body mass index ≥ 40 kg/m^2) and 95 normal weight patients with normal OGTT [fasting plasma glucose (FPG) < 100 mg/dL. Two-hour glucose during OGTT < 140 mg/dL] were evaluated in this study.

Results: The mean $\pm$ SD NLR of MOP was significantly higher than that of patients with normal weight healthy patients (3.67 ± 0.95 vs. 1.82 ± 1.02, $P < 0.001$, respectively). In receiver operating characteristics curve analysis, NLR > 3.12 had 79.2% sensitivity and 64.9% specificity in predicting T2DM. Logistic regression analysis showed that elevated NLR (OR: 2.577, 95% CI: 1.363–4.872, $P = 0.004$) was an independent variable for predicting T2DM in MOP.

Conclusions: MOP have higher NLR than healthy controls. High NLR is a powerful and independent predictor of T2DM in MOP. Elevated NLR levels are usually considered as an inflammatory marker. The results of this study suggested that inflammation plays a role in the pathogenesis of T2DM with MOP.

1. Introduction

The prevalence of obesity has increased throughout the last three decades due to genetic, metabolic, behavioral, and environmental factors [1]. Obesity in turn increases risk for a number of metabolic diseases including type 2 diabetes, cardiovascular disease, fatty liver disease and some forms of cancer [1]. Despite the well-known link between obesity and increased morbidity, the mechanism of this remains elusive. Obesity is the hallmark of the metabolic syndrome and predisposes patients to the development of major chronic metabolic diseases including type 2 diabetes mellitus. Adipose tissue expansion in obesity is characterized by increasing infiltration of proinflammatory immune cells into adipose tissue causing chronic, low-grade inflammation. It now appears that, in most obese patients, obesity is associated with a low-grade inflammation of white adipose tissue (WAT) resulting from chronic activation of the innate immune system and which can subsequently lead to insulin resistance, impaired glucose tolerance and even diabetes [2]. Obesity and metabolic syndrome are associated with a low-grade, chronic (smoldering) state of inflammation characterized by increased circulating free fatty acids and chemoattraction of immune cells (such as macrophages that also produce inflammatory mediators) into the local milieu. These effects are further amplified by the release of inflammatory cytokines such as interleukin (IL)-1β, IL-6, TNF-α, and monocyte chemoattractant protein (MCP)-1 [2]. Adipocytes can enlarge past the point of effective oxygen diffusion, which results in hypoxia and eventually necrosis. Free fatty acids

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; F, female; FPG, fasting plasma glucose; HC, hip circumference; HDL, high-density lipoprotein; HT, hypertension; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; M, male; MOP, morbid obesity patients; MS, metabolic syndrome; NLR, neutrophil-to-lymphocyte ratio; OGTT, oral glucose tolerance test; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TG, triglycerides; WAT, white adipose tissue; WC, waist circumference; WHR, waist hip ratio.

* Corresponding author at: Turgut Ozal University School of Medicine, Department of Internal Medicine, 06510 Beştepe, Ankara, Turkey. Tel.: +90 312 2035555; fax: +90 312 3186690.
E-mail address: drhakkiyilmaz@yahoo.com (H. Yilmaz).

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escape the engorged/necrotic adipocytes and deposit in other tissues, which in turn promotes insulin resistance and diabetes (through downregulation of insulin receptors and glucose transporters). Several factors derived not only from adipocytes but also from infiltrated macrophages probably contribute to the pathogenesis of insulin resistance. Most of them are overproduced during obesity, including leptin, TNF-alpha, IL-6 and resistin. Conversely, expression and plasma levels of adiponectin, an insulin-sensitising effector, are down-regulated during obesity. Leptin could modulate TNF-alpha production and macrophage activation. TNF-alpha is overproduced in adipose tissue of several rodent models of obesity and has an important role in the pathogenesis of insulin resistance in these species.

Development of diabetes in obesity is of multifactorial origin. However, inflammation is among the most important factors. It is known that various inflammatory markers predict development of type 2 diabetes. NLR is a simple and inexpensive index of systemic inflammatory burden that correlates with prognosis in distinct disease states. It has been generally investigated in inflammatory, cardiovascular and neoplastic diseases. It has been reported that NLR level is significantly correlated with metabolic syndrome criteria. However, no study has investigated any possible association between NLR and prediction of T2DM in MOP. The aim of the present study was to investigate the predictive value of NLR on development of T2DM in morbid obesity patients (MOP).

2. Materials and methods

This retrospective study evaluated the diagnostic value of NLR for T2DM in 306 Morbid Obesity patients are recorded at the Diskapi Yildirim Beyazit Training and Research hospital between February 2009 and July 2011. The control group consisted of 95 normal weight healthy, age and gender matched subjects (male/female: 11/84). We did not apply local ethical committee for this study. Because this study is retrospective. All the guidelines of Helsinki were followed.

Patients with the following were excluded from the study: patients with prior history of type 1, 2 diabetes mellitus, patients with a recent acute coronary syndrome (<3 months), patients treatment with corticosteroids and those with any evidence of active infection, peritonitis, pancreatitis, pelvic inflammatory disease, cancer, chronic liver disease, leukocytosis (>12.000/μL), leucopenia (<3.500/μL), cushing syndrome (with dexamethasone suppression tests) and fever. Overweight is defined as a body mass index (BMI) of 25–29.9 kg/m^2, obesity as a BMI $\geq$ 30 kg/m^2, and morbid obesity as a BMI $\geq$ 40 kg/m^2. We enrolled 306 morbid obesity patients in this study. 75 g oral glucose tolerance test (OGTT) was performed for all morbid obesity patients to diagnose T2DM. We accepted the definitions of ADA report [normal—fasting plasma glucose (FPG) <100 mg/dL (5.6 mmol/L). Two-hour glucose during OGTT <140 mg/dL (7.8 mmol/L). Impaired fasting glucose (IFG)—fasting plasma glucose between 100 and 125 mg/dL (5.6–6.9 mmol/L). Impaired glucose tolerance (IGT)—2-h plasma glucose value during a 75 g oral glucose tolerance test between 140 and 199 mg/dL (7.8–11.0 mmol/L). Diabetes mellitus—FPG at or above 126 mg/dL (7.0 mmol/L), a 2-h value in an OGTT (2-h PG) at or above 200 mg/dL (11.1 mmol/L)]. The following data were extracted from the hospital database: age, sex, body weight (in kg), height (in meters), waist/hip ratio, drug intake, smoking, hypertension and other medical history. We calculated body mass index (BMI) = body weight (in kg)/height (in meters) squared. Only patients with morbid obesity (obesity grade III; BMI $\geq$ 40 kg/m^2) were included in the present study. Arterial hypertension was defined by systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 or the use of antihypertensive medication.

Laboratory tests included fasting lipid profile (which included total cholesterol fasting triglyceride, and HDL cholesterol, with LDL cholesterol calculated from these if the fasting triglyceride was <400 mg/dl), fasting plasma glucose, and liver function tests. Complete blood count (CBC) was also recorded for each MOP. All CBC analysis was performed in the hematology laboratory of our hospital. CBC analysis was performed with the same analyzer within 1 h of collection of blood samples with the use of a Coulter Counter technique (Coulter Gen-S Hematology Analyzer, Beckman Coulter Corp, Hialeah, Florida).

Analyses were performed using SPSS 17.0 (SPSS, Inc., Chicago, Illinois). Values were presented as mean ± standard deviation or, in the case of non-normally distributed data, as median and range. To test the distribution pattern, the Kolmogorov–Smirnov test was used. The study population was assigned into tertiles based on NLRs at admission. The patients were categorized into 3 equal tertiles according to their baseline 33rd and 66th NLR percentiles obtained from our data were NLR < 3.04, 3.04 $\leq$ NLR $\leq$ 4.03, and NLR > 4.03. For non-normally distributed variables, comparisons between groups were performed using the Mann–Whitney *U* test, whereas unpaired Student's *t* tests were used for comparisons among normally distributed variables. Comparisons of multiple mean values were carried out by Kruskal–Wallis tests or analysis of variance as appropriate. Categorical variables were summarized as percentages and compared with chi-square test. Spearman correlation coefficient was computed to examine the association between 2 continuous variables. Forward stepwise multivariate logistic regression models were created to identify independent predictors of T2DM. Receiver operating characteristic (ROC) curve analysis was used to identify optimal cut-off value of NLR with maximum sensitivity and specificity for development of T2DM in MOP. Two-tailed *P*-values of less than 0.05 were considered to indicate statistical significance.

3. Results

Totally, 306 patients with Morbid Obesity and 95 age- and sex-matched participants were included in the study as patient and control groups, respectively. Clinical and biochemical characteristics of both groups are summarized in Table 1. The mean age of the MOP and control group were 46.37 ± 11.24 years and 45.82 ± 10.93 years, respectively. After OGTT, 101 morbid obesity patients had T2DM (33%). According to age and gender, there was no difference between groups. Comparisons of laboratory parameters among MO patients with or without T2DM are shown in Table 2.The mean NLR values of MO patients and controls were 3.67 ± 0.95 and

Table 1
Demographic and laboratory features of morbid obesity patients and controls.

	MOP n = 306	Control group n = 95	*P*
Age (year)	46.37 ± 11.24	45.82 ± 10.93	0.911
Gender, female, % (F/M, n)	89.9 (275/31)	89.4 (85/10)	0.945
WC, cm	111.31 ± 11.02	81.39 ± 12.95	<0.001
HC, cm	133.60 ± 9.39	88.18 ± 9.45	<0.001
WHR	0.83 ± 0.7	0.80 ± 0.9	0.432
BMI, kg/m^2	45.61 ± 5.79	21.32 ± 3.75	<0.001
Current smoker, % (n)	23 (71)	0	<0.001
SBP, mmHg	138 ± 12	108 ± 11	<0.001
DBP, mmHg	91 ± 14	75 ± 10	<0.001
HT, % (n)	53.9 (165)	0	<0.001
DM, % (n)	33 (101)	0	<0.001
FBG, mg/dl	115.27 ± 17.56	78.45 ± 15.62	<0.001
HDL, mg/dl	41.45 ± 10.27	46.38 ± 7.23	0.321
LDL, mg/dl	128.10 ± 26.17	92.12 ± 10.45	<0.001
TG, mg/dl	182.67 ± 77.79	128.78 ± 25.51	0.03
NLR	3.67 ± 0.95	1.82 ± 1.02	<0.001

Abbreviations: F, female; M, male; WC, waist circumference; HC, hip circumference; WHR, waist hip ratio; BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; MOP, morbid obesity patients; FBG, fasting blood glucose; HDL, high-density lipoprotein; HT, hypertension; LDL, low-density lipoprotein; SBP, systolic blood pressure; TG, triglycerides; NLR, neutrophil–lymphocyte ratio.