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Assessment of the relationship between insulin resistance, atherogenic index of plasma and white blood cell count: A data mining study

İnsülin direncinin plazma aterojenik indeks ve beyaz küre sayısı ile ilişkisinin değerlendirilmesi: Bir veri madenciliği çalışması

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SUMMARY

Objective: The hyperinsulinemic-euglycemic clamp tests considered as a gold standard method for assessing the insulin sensitivity, whereas the application of this test in large groups is both difficult and not practical, therefore clinicians need calculating parameters to evaluate the insulin sensitivity. In the study we evaluated the prediction of insulin resistance (IR) by atherogenic index of plasma (AIP) and WBC count.

Method: We retrospectively reviewed the records of 139.934 individuals admitted to our hospital from March 2015 to March 2016. 474 individuals were enrolled in our study. Study population's records such as age, gender, white blood cell (WBC) count and the concentrations of overnight fasting blood glucose, triglyceride (TG), total cholesterol (TCHOL), HDL-C, low density lipoprotein cholesterol (LDL-C) and insulin were recorded from our hospital information system.

Results: The receiver operating characteristic curves (AUC) of AIP for predicting IR were 0.670 and 0.690 as measured by homeostatic model assessment-insulin resistance (HOMA-IR) and insulin sensitivity check index (QUICKI), respectively. The area under the curve (AUC) values for predicting IR with WBC count were 0.649 and 0.652 as measured by HOMA-IR and QUICKI, respectively.

Conlusions: Negative predictive values of AIP and WBC were found higher than positive predictive values as measured HOMA-IR. AIP and WBC may not serve as a predictor of IR lonely but these markers might be used as surrogate markers may contribute to excluding IR when used in combination with HOMA-IR and QUICKI.

Keywords : Atherogenic index of plasma, WBC count, Insulin resistance, Triglyceride, HDL

ÖZET

Amaç: Hiperglisemik öglisemik klemp testi insülin direncinin (İD) değerlendirilmesinde altın standart olarak kabul edilmektedir. Bununla birlikte bu testin geniş gruplarda uygulanması zor ve pratik değildir. Bu nedenle klinisyenler İD'nin değerlendirilmesinde hesaplamalı parametrelere ihtiyaç duymaktadır. Bu çalışmada insulin direncinin değerlendirilebilmesinde plazma aterojenik indeks (PAİ) ve beyaz küre (WBC) değerinin kullanılıp kullanılamayacağı tespit edilmeye çalışılmıştır.

Yöntem: Bu amaçla Mart 2015- 2016 yılları arasında Cumhuriyet Üniversitesi Sağlık Hizmetleri Araştırma ve Uygulama Hastanesi'ne başvuran 138.934 kişinin bilgileri incelendi ve 474 kişi çalışmaya dahil edildi. Çalışma populasyonuna ait yaş, cinsiyet, WBC sayısı, açlık glukoz, trigliserid, total kolesterol, yüksek dansiteli lipoprotein kolesterol ve insulin düzeyi bilgileri hastane bilgi işlem sisteminden alındı.

Bulgular: İD'nin varlığının gösterilmesinde PAİ için elde edilen eğri altında kalan alan (AUC) değerleri homeostatic model assessment-insuline resistance (HOMA-IR) ve quantitative insulin sensitivity check index (QUICKI) için sırasıyla 0.670 ve 0.690 olarak tespit edildi. Bu değerler WBC için sırasıyla 0.649 ve 0.652 olarak bulundu. Ayrıca HOMA-IR değeri baz alındığında **PAİ** ve WBC'nin negatif prediktif değerinin pozitif prediktif değerinden daha yüksek olduğu görüldü.

Sonuç: İnsulin direncinin tespitinde WBC ve AIP'in tek başına kullanılabilecek güvenilir bir belirteç olmadığı ancak bu parametrelerin HOMA-IR ve QUICKI ile birlikte insulin direncinin dışlanmasına katkı sağlayabileceği düşünülmektedir.
Anahtar sözcükler: Plazma aterojenik indeks, WBC, insulin direnci, trigliserid, HDL

INTRODUCTION

The insulin resistance (IR) is increasingly recognized as a serious, worldwide public health problem and it is associated with central obesity, impaired glucose tolerance, diabetes mellitus, hypertension, dyslipidemia and cardiovascular disease (CVD)[1]. The hyperinsulinemic-euglycemic clamp test was considered as a gold standard method for assessing the insulin sensitivity, whereas the application of this test in large groups is both difficult and not practical, therefore calculated parameters such as homeostatic model assessment-insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) has been emerged to evaluate the insulin sensitivity[2,3]. HOMA-IR has been widely used in the routine clinical assessment of patients with metabolic syndrome, however, because of the lack of standardization of insulin assay ıt has limited clinical utility[4].

White blood cell (WBC) count is an indicator of the activation of inflammation and immune system[5,6]. Although, It has been proposed that the circulating WBC is one of the biomarkers for the predicting of cardiovascular risk and insulin resistant states[5,7], the predictive ability of WBC count has not been fully explored for the prediction of IR and cardiovascular disease[5,8,9]. Hypertriglyceridemia and low high density lipoprotein cholesterol (HDL-C) concentrations which are two important serum lipid abnormalities associated with IR[10,11]. The triglyceride (TG) to HDL-C ratio has been used as a predictor of IR[12,13]. However, some limitations have been reported on the use of TG/HDL-C ratio for evaluating IR[14-16]. Atherogenic index of plasma (AIP) which is the logarithmic transformation of the TG to HDL-C ratio (AIP = log TG/HDL-C) predicts the risk of atherosclerosis[17]. So far there are no data on the association between AIP and insulin sensitivity.

This study was set out with the aim of evaluating the prediction of IR by AIP and WBC count. We also aimed to evaluate the change of WBC counts according to different HDL-C and (TG) concentrations. In reviewing the literature, no data was found on the use of AIP and WBC count for assessing IR and evaluating the change of WBC counts in different HDL-C and TG concentrations.

MATERIAL AND METHODS

Study subjects

Study population were composed of 331 (69.8%) female and 143 (30.2%) male individuals. The average ages of individuals were 37.78 years (from 18 to 82 years). None of the participants had diabetes mellitus. Exclusion criteria in the study population included clinical suspicion of infections (body temperature out of the range between 36- 38 $^{\circ}$C, heart rate > 90 rate/minute, respiratory rate > 20/minute, WBC count> $12x10^3$mcL or < $4x10^3$mcL), presence of liver diseases, kidney diseases, rheumatic disease, malignancy, pregnancy, cardiovascular disease, impaired thyroid functions, body mass index $\geq$ 25 and taking lipid lowering drugs. Individual's records such as age, gender, WBC count and the concentrations of overnight fasting blood glucose, TG, total cholesterol (TCHOL), HDL-C, low density lipoprotein cholesterol (LDL-C) and insulin were obtained from Cumhuriyet University Hospital's laboratory information system. The protocol was approved by Cumhuriyet University Ethical Committee (2016-10/15).

Study design

In this study, we retrospectively reviewed the records of 139.934 individuals admitted to our hospital from March 2015 to March 2016. 474 individuals were enrolled to our study. To determine the affected parameters from IR study population was divided to four sub-groups according to the HOMA-IR and QUICKI index values. Threshold values for HOMA-IR and QUICKI were determined according to the studies made by Yamada et al.[18], Salgado et al.[19] and McAuley et al.[20]. We also investigated the use of WBC count and AIP for predicting the IR. Finally, we evaluated the change of WBC counts in the presence of different HDL-C and TG concentrations which are determined according to American Association of Clinical Endocrinologist's guidelines[21].

Biochemical analysis and determination of AIP, HOMA-IR and QUICKI

Complete Blood Count analysis was performed using hematology system (Mindray BC6800, China). Fasting blood glucose, TG, TCHOL, HDL-C and LDL-C concentrations were determined by enzymatic colorimetric method (Beckman Coulter AU5800, USA). Serum insulin concentrations

were measured by using chemiluminescence immunoassay (Beckman Coulter Unicel DxI 800, USA). We calculated AIP, HOMA-IR and QUICKI values according to following formula; AIP: [log TG/HDL-C] (17), HOMA-IR: [fasting plasma glucose (mg/dL) X fasting serum insulin (μIU/mL)/405][22] and QUICKI: [1 / (log(fasting insulin μU/mL) + log(fasting glucose mg/dL)][23].

Statistical analysis

The Shapiro-Wilk's test was used and histogram and q-q plots were examined to assess the data normality. Accordingly Mann-Whitney U tests were used to compare the differences of continuous variables between binary groups. Receiver operating characteristic (ROC) curves were plotted for the WBC and AIP to detect the predictive performance of HOMA-IR and QUICKI. The area under curves and also, cut-offs were determined for each variable. Sensitivity, specificity, positive predictive rate, negative predictive rate, positive likelihood ratio, negative likelihood ratio and area under curve diagnostic measures were calculated. R 3.2.2 softwares were used for all analyses. A $p<0.05$ probability level was considered statistically significant.

RESULTS

Comparison of the values of fasting blood glucose, AIP, WBC and serum lipids according to different HOMA-IR and QUICKI indices values were given in Table 1. We found positive correlation between WBC count, HOMA-IR ($p < 0.001$, r= 0.222) AIP ($p < 0.001$, r= 0.247), insulin ($p < 0.001$, r= 0.255) and TG ($p < 0.001$, r= 0.209), however, negative correlation was found between WBC count, QUICKI ($p < 0.001$, r= - 0.258) index and HDL-C ($p < 0.001$, r= - 0.264). We also found positive correlation between AIP, HOMA-IR ($p < 0.001$, r= 0.287) and insulin ($p <0.001$, r = 0.276) however, negative correlation were observed between AIP and QUICKI ($p <0.001$, r = -0.378).Comparison of WBC counts according to different threshold values for HDL-C and TG concentrations were given in Table 2. We also evaluate the diagnostic performance of WBC and AIP for predicting the IR using different threshold values for QUICKI and HOMA-IR. Diagnostic measures and threshold values of WBC and AIP were given in Table 3. The area under the ROC curves (AUC) for AIP and WBC count were given in Fig 1.

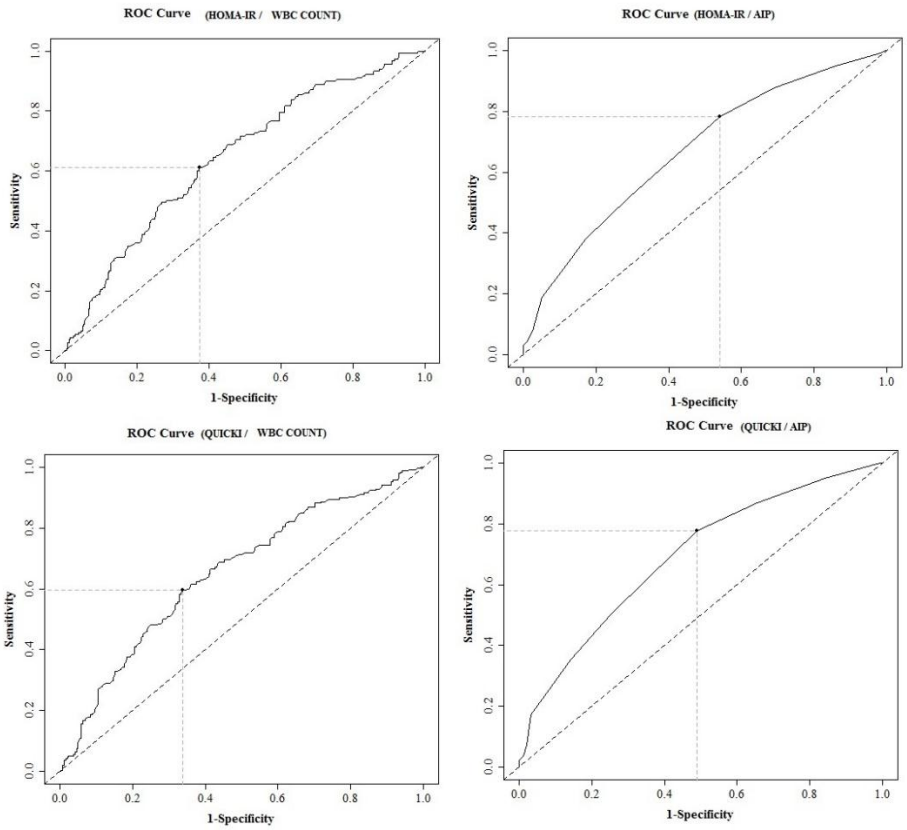

Figure 1. The area under the ROC curves for AIP and WBC count. A: represent the ROC curve for WBC count as measured by HOMA-IR, B: represent the ROC curve for AIP as measured by HOMA-IR, C: represent the ROC curve for WBC count as measured by QUICKI, D: represent the ROC curve for AIP as measured by QUIC

Table 1. Comparison of the values of median fasting blood glucose, AIP, WBC count and serum lipids according to different HOMA-IR and QUICKI indices

HOMA-IR	***< 2.5 (n:293)***	***≥ 2.5 (n:181)***	P
AIP	0.3 (0.1-0.5)	0.5 (0.3-0.7)	<0.001
WBC count (10^3 mcL)	6.39 (5.5-7.5)	7.3 (6.2-8.3)	<0.001
FBG (mg/dL)	90.0(84.0-95.0)	98.0(90.0-109.0)	<0.001
TG (mg/dL)	92.5 (68.0-141.0)	132.5(88.3-192.0)	<0.001
TCHOL (mg/dL)	192.0(168.0-223.5)	195.5(166.0-223.8)	=0.712
HDL-C (mg/dL)	52.0(43.0-60.0)	45.0(38.3-53.8)	<0.001
LDL-C (mg/dL)	130.0(108.8-154.0)	130.5(107.0-151.5)	=0.859
QUICKI	***< 0.33 (n:237)***	***≥ 0.33 (n:237)***	
AIP	0.5(0.3-0.7)	0.2(0.1-0.5)	<0.001
WBC count (10^3 mcL)	7.3(6.1-8.3)	6.2 (5.4-7.3)	<0.001
FBG (mg/dL)	97.0(89.5-104.5)	89.0(84.0-94.0)	<0.001
TG (mg/dL)	128.0(88.0-189.5)	87.0(66.0-136.0)	<0.001
TCHOL (mg/dL)	192.0(167.0-223.0)	193.0(168.0-225.0)	=0.466
HDL-C (mg/dL)	45.0(38.5-54.0)	53.0 (44.0-61.0)	<0.001
LDL-C (mg/dL)	130.0 (108.5-149.0)	131.0(108.0-155.0)	=0.843

AIP: Atherogenic index of plasma, FBG: Fasting blood glucose, HDL-C: High density lipoprotein cholesterol, HOMA-IR: Homeostatic model assessment-insulin resistance, LDL-C: Low density lipoprotein cholesterol, QUICKI: International normalization ratio WBC: white blood cell, TCHOL: Total cholesterol, TG: Triglyceride. Results are expressed as median (25^{th}-75^{th} percentile) with 95% confidence intervals.

Table 2. Comparison of WBC values according to HDL-C and TG concentrations

HDL-C(mg/dL)	***< 60 (n: 378)***	***≥ 60 (n:96)***	P
WBC count (10^3 mcL)	6.95(5.90-8.02)	6.29 (5.30-7.37)	<0.001
HDL-C (mg/dL)	***≤ 40 (n:103)***	***>40 (n:371)***	
WBC count (10^3 mcL)	7.34 (6.13-8.38)	6.66 (5.65-7.66)	<0.001
TG (mg/dL)	**< 150 (n:339)**	**≥ 150 (n:135)**	
WBC count (10^3 mcL)	6.70 (5.65-7.70)	6.99 (6.10-8.18)	p=0.011

HDL-C:High density lipoproteins cholesterol, TG: Triglyceride, WBC: White blood cell. Results are expressed as median (25^{th}-75^{th} percentile) with 95% confidence intervals.

Tablo 3. Statistical diagnostic measures of white blood cell count and atherogenic index of plasma for HOMA-IR and QUICKI

Variable	Diagnostic measures						Area under ROC curve	
	SEN(95%CI)	**SPE(95%CI)**	**PPR(95%CI)**	**NPR(95%CI)**	**LR+(95%CI)**	**LR-(95%CI)**	**AUC**	***p***
HOMA-IR								
WBC (>6.94)	0.61(0.54-0.68)	0.63(0.57-0.68)	0.50(0.44-0.58)	0.72(0.66-0.77)	1.63(1.35-1.97)	0.62(0.51-0.76)	0.649	<0.001
AIP (>0.30)	0.78(0.72-0.84)	0.46(0.40-0.52)	0.47(0.41-0.57)	0.78(0.71-0.81)	1.45(1.27-1.65)	0.47(0.35-0.64)	0.670	<0.001
QUICKI								
WBC (>6.94)	0.60(0.53-0.66)	0.66(0.60-0.72)	0.64(0.57-0.70)	0.62(0.56-0.68)	1.76(1.43-2.17)	0.61(0.51-0.73)	0.652	<0.001
AIP (>0.30)	0.78(0.72-0.83)	0.51(0.45-0.58)	0.61(0.55-0.69)	0.70(0.63-0.75)	1.59(1.37-1.84)	0.49(0.34-0.57)	0.690	<0.001

SEN: Sensitivity; SPE: Specificity; PPR: Positive predictive rate; NPR: Negative predictive rate; LR+: Positive likelihood ratio; LR-: Negative likelihood ratio; AUC: Area under curve, ROC: Receiver operating charecteristics

DISCUSSION

This study aimed to develop a simple predictive model as a clinical tool for evaluation of IR. Therefore, we proposed the prediction of IR by AIP and WBC count. Whereas several studies investigated the use of TG/HDL-C ratio for predicting IR there is not any study on the use of AIP for evaluating the IR. The study made by McLaughlin et al.[13] reported that TG/HDL-C ratio offer the most practical approach to identify IR. Kimmet al.[24] indicated that TG/HDL-C was a consistent indicator of IR in subjects without metabolic syndrome. It was also reported that TG/HDL-C was not a reliable predictor for IR because of racial differences[14,15]. The current study found positive correlation between AIP and HOMA-IR. Additionally we found negative correlation between AIP and QUICKI. In this study the receiver operating characteristics of AIP for predicting IR were 0.670 and 0.690 as measured by HOMA-IR and QUICKI, respectively. In our study threshold value of AIP for determining IR was determined as 0.3. Additionally negative and positive predictive values of this threshold value were 0.78 and 0.47, respectively. In the studies made by Kannel et al.[25] and Kim-Dorner et al.[14] the AUC of TG/HDL-C were found to be 0.77 and 0.75. Our AUC values were found lower than the other studies. We think that AIP is not a reliable marker that can be used alone to detect the IR. However the negative predictive value of this marker was found higher than positive predictive value. Therefore we think that AIP might be useful in excluding IR when used in combination with HOMA-IR and QUICKI.

White blood cell count has been shown as a risk factor for cardiovascular disease. Decreased insulin sensitivity has been suggested as the link between WBC count and cardiovascular disease[26]. Several studies reported that the positive correlation between WBC count and IR[5,27]. Whereas there is not any study on the use of WBC count for predicting IR. Chaoet al.[28] found that the threshold value of WBC count for predicting the future metabolic syndrome was 5 x 10^3 mcL. Oda et al.[29] reported that the WBC count threshold values were 5x10^3mcL and 5.63 x 10^3mcL for women and men to predict the metabolic syndrome, respectively. Twig et al.[27] reported that WBC count above 6.9 x 10^3 mcL had an independent 52% increase in diabetes risk compared with the lowest quintile. We found that individuals whose WBC count greater than 6.93 x 10^3 mcL are more insulin resistant than the others having WBC count less than 6.93 x 10^3 mcL. Positive and negative predictive value of this threshold values were found as 0.50 and 0.72. The threshold value proposed by Twig et al[27] were similar to ours value. In the present study the AUC values for predicting IR with WBC count were 0.649 and 0.652as measured by HOMA-IR and QUICKI, respectively. We think that as in the AIP, WBC count is not a reliable marker that can be used alone in evaluating IR due to low AUC values. Whereas WBC count might be useful in excluding IR when used in combination with HOMA-IR and QUICKI in non-obese and non-diabetic individuals.

Insulin resistance is a major risk factor for diabetes, metabolic syndrome and cardiovascular disease[30]. Dyslipidemia associated with IR play an important role in accelerated atherosclerotic cardiovascular disease[25]. IR significantly impacts on the concentrations of TG and HDL-C. It has been reported that high concentrations of TG, low concentrations of HDL-C and unchanged concentrations of TCHOL and LDL-C in case of IR[10,12,31-36]. Similar to these findings we have found higher TG concentrations, lower HDL-C concentrations, unchanged LDL-C and TCHOL concentrations in persons who have the values of HOMA-IR $\geq$ 2.5 and OUICKI < 0.33. Our findings match those observed in earlier studies. Isolated low HDL-C concentrations are seen rarely and this situation is generally associated with genetic disorders[37]. Many investigators have postulated that hypertriglyceridemia combined with action of hepatic lipase forces in the reduction of HDL-C in IR state [31,37]. Another potential mechanism for the reduced HDL-C concentrations in hypertriglyceridemic insulin resistant state is the affected cholesterol transfer metabolism between TG rich lipoprotein and HDL-C rich lipoproteins[38,39]. In this study we found statistically significant difference in terms of WBC count between individuals grouped according to different TG and HDL-C concentrations. Although the low r value we also found positive correlation between the values of WBC count, AIP, HOMA-IR, TG and insulin and also we found negative correlation between HDL-C, QUICKI. Talukdar et al.[40] discovered that an enzyme secreted by neutrophils called neutrophil elastase impairs insulin signaling and boosts IR. Taken together, our results suggest that the increase of WBC count within the reference range affects the concentrations of TG and HDL-C by disrupting the cellular insulin response in non-diabetic and non-obese persons.

The main limitation of this study is that the lack of information on smoking, alcohol intake, regular physical exercise, and family history of diabetes status of the study population. In addition, the relatively homogeneous ethnic group and

environment to which participants in our study were exposed might reduce the effect of unknown confounders.

CONCLUSION

AIP and WBC may not serve as a predictor of IR lonely but these markers might be used as surrogate markers for excluding IR when used in combination with HOMA-IR and QUICKI. The changes in WBC count within normal ranges are associated with the concentrations of HDL-C and TG in nondiabetic and normal weight individuals. Future research is warranted to assess the use of AIP and WBC count for predicting IR in a larger population.

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