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Original Article / Orijinal Araştırma

Association Between Atherogenic Index of Plasma, Blood Pressure and Impaired Glucose Metabolism; Results of Diabetes Screening in a Tertiary Healthcare Center

Plazma Aterojenik İndeksi, Kan Basıncı ve Bozulmuş Glikoz Metabolizması Arasındaki İlişki; Üçüncü Basamak Sağlık Merkezinde Diyabet Taraması Sonuçları

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ABSTRACT

Objective: Atherogenic index of plasma (AIP) is a relatively new index used to predict the risk of cardiovascular diseases in the general population. AIP has been shown to be associated with increased fasting plasma glucose (FPG) levels, diabetes mellitus, and metabolic syndrome. However, to the best of our knowledge, no study has investigated the relationship between AIP and impaired glucose metabolism using oral glucose tolerance test and hemoglobin A1c (HbA1c) level.

Materials and Method: AIP was calculated using the formula involving the logarithm of the molar ratio of triglyceride to high-density lipoprotein cholesterol. The association among AIP, glucose metabolism parameters, and diabetes status was analyzed.

Results: The frequency of prediabetes and diabetes among the study subjects was 48.2% (n=216) and 20.5% (n=92), respectively. Overall, 52.7% of the subjects were in the low-risk group (AIP<0.11), 12.5% in the intermediate-risk group (AIP 0.11–0.21), and 34.8% in the high-risk group (AIP>0.21). An increased AIP (high-risk group) was significantly associated with prediabetes and diabetes. AIP was also significantly correlated with systolic and diastolic blood pressures and HbA1c, FPG, and 2-hour plasma glucose levels.

Conclusions: AIP was significantly associated with the parameters of diabetes and metabolic syndrome. Simple calculations from fasting lipid panel results may provide further information to evaluate the risk of cardiovascular diseases risk in patients with prediabetes and diabetes.

Keywords: Cardiovascular disease, diabetes mellitus, prediabetic state, dyslipidemia

ÖZ

Amaç: Aterojenik plazma indeksi (AIP), genel popülasyonda kardiyovasküler hastalık riskini tahmin etmek için kullanılan nispeten yeni bir indekstir. AIP'nin yüksek açlık plazma glukoz (FPG) seviyeleri, diabetes mellitus ve metabolik sendrom ile ilişkili olduğu gösterilmiştir. Bununla birlikte, literatür taramamıza göre, oral glukoz tolerans testi ve hemoglobin A1c (HbA1c) düzeyi kullanılarak AIP ile bozulmuş glukoz metabolizması arasındaki ilişkiyi araştıran bir çalışma yapılmamıştır.

Gereç ve Yöntem: AIP, trigliseritin yüksek yoğunluklu lipoprotein kolesterole molar oranının logaritmasını içeren formül kullanılarak hesaplandı. AIP, glikoz metabolizması parametreleri ve diyabet durumu arasındaki ilişki analiz edildi.

Bulgular: Çalışma katılımcıları arasında prediyabet ve diyabet sıklığı sırasıyla %48,2 (n=216) ve %20,5 (n=92) idi. Genel olarak, katılımcıların %52,7'si düşük risk grubunda (AIP<0,11), %12,5'i orta risk grubunda (AIP 0,11-0,21) ve %34,8'i yüksek risk grubunda (AIP>0,21) idi. Yüksek AIP (yüksek risk grubu), prediyabet ve diyabet ile önemli ölçüde ilişkiliydi. AIP ayrıca sistolik ve diyastolik kan basınçları ve HbA1c, FPG ve 2 saatlik plazma glukoz seviyeleri ile önemli ölçüde ilişkiliydi.

Sonuçlar: AIP, diyabet ve metabolik sendrom parametreleri ile önemli ölçüde ilişkiliydi. Açlık lipid paneli sonuçlarından basit hesaplamalar, prediyabet ve diyabetli hastalarda kardiyovasküler hastalık riskini değerlendirmek için daha fazla bilgi sağlayabilir.

Anahtar Kelimeler: Kardiyovasküler hastalık, diabetes mellitus, prediyabetik durum, dislipidemi

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INTRODUCTION

Coronary artery disease (CAD) is a multifactorial disorder in which several environmental and genetic factors play a role in the pathogenesis. Obesity, hypertension, cigarette smoking, prediabetes, diabetes, dyslipidemia, physical inactivity, and psychosocial stress are several of the well-defined modifiable risk factors for CAD (1, 2). Multiple pathophysiologic mechanisms underlie the relationship between impaired glucose metabolism and the development of CAD. Diabetic dyslipidemia was one of the major components of this complex relationship.

Measurement of plasma lipid and lipoprotein levels is the simplest method to determine dyslipidemia. However, defining dyslipidemia with the use of classical methods has several shortcomings. For instance, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) particle sizes are independently associated with atherogenesis and classical methods lack the ability to estimate particle sizes. Therefore, development of assays for the evaluation of lipoprotein subclasses has significantly contributed to the estimation of cardiovascular risk. Recent studies indicated that a calculable equation with triglyceride (TG) and HDL-C levels can be used for prediction of cardiovascular risk (3). AIP is accounted as log (TG/HDL-C) and it has been described as a predictor of CAD (4, 5) and indicator of small LDL particle size (3, 5, 6). A recent retrospective study demonstrated that elevated fasting blood glucose levels were associated with higher AIP (7). Additionally a large prospective study from Turkey showed that AIP predicts type-2 diabetes mellitus, metabolic syndrome and hypertension (8). However, according to our extensive literature search there has been no study done to assess the relationship between AIP, impaired glucose metabolism and diabetes status (non-diabetic, prediabetic and diabetic subjects) determined by oral glucose tolerance test (OGTT) and HbA1c. Therefore, this study purposed to determine the association between AIP and impaired glucose metabolism by conducting OGTT and measuring HbA1c levels in high risk population.

MATERIALS AND METHODS

Study subjects were prospectively enrolled from outpatient clinic and consisted of individuals who presented to the clinic for diabetes screening or who were referred by family physicians for the same reason. Previously healthy individuals who were between the ages of 18 and 80 years and who were at risk for diabetes according to actual American Diabetes Association criteria were included in the study. Individuals who has chronic medical diseases or those who was using any medications were excluded from the study. American Diabetes Association diabetes diagnostic criteria were used to define prediabetes and diabetes. According to FPG levels, OGTT results (after application of 75 g oral glucose) and HbA1C levels, study subjects were categorized into 3 groups: non-diabetic (all of the following; FPG <100 mg/dL, 2-h plasma glucose <140 mg/dL, HbA1c <5.7%), prediabetic (at least one of the following after excluding diabetes; FPG 100 to 125 mg/dL, 2-h plasma glucose 140 to 199 mg/dL, HbA1c 5.7 to 6.4%), and diabetic (at least one of the following; fasting glucose ≥126 mg/dL, 2-h plasma glucose ≥200 mg/dL, HbA1c ≥6.5%).

AIP was counted up as the logarithmically transformed molar ratio of the TG to HDL-C [log (TG/HDL-C)] measured in mmol/L. According to AIP results and regarding previous literature reports subjects were grouped into three groups: low (<0.11), intermediate (0.11-0.21) and increased (>0.21) risk (9, 10).

The systolic blood pressure (SBP) and diastolic blood pressure (DBP) readings were determined properly using an Erka sphygmomanometer (PMS Instruments Limited, Berkshire, UK). The mean value of two records was used for analysis.

Body-mass index (BMI) was determined as body weight in kilograms divided by the square of the height in meters. Weight and height were measured properly with the lightest possible clothing and without shoes.

Venous blood samples were drawn after at least 10 hours of fasting. All biochemical analyses were performed in the Central Biochemistry Laboratory.

Total cholesterol (TC), HDL-C and TG levels were measured using an oxidase-based technique by the Beckman Coulter AU 2700 plus, Missima, Japan. LDL-C was calculated by Friedewald formula. HbA1c was measured by high performance liquid chromatography (HPLC) method using the Adams HA-8160 (Shiga, Japan).

Descriptive statistics for each variable were estimated. Normality of the data distribution was assigned with the Kolmogorov-Smirnov test. Continuous variables with normal distributions were expressed as mean ± SD. Non-parametric statistics (Mann–Whitney U or Kruskal-Wallis) and parametric statistics (t test, ANOVA) were all used for continuous variables, properly. For categorical variables, chi-square test was used to determine statistical significant differences between the groups. Pearson correlation and Spearman's rho (for data that was not normally distributed) tests were used to determine correlations between the variables. Linear regression analysis with backward elimination was also performed to define variables associated with AIP. Two-sided p values less than 0.05 were considered significant.

RESULTS

The variables of the 448 individuals included in the study are shown in Table 1. Subjects were predominantly female

(78%) with a mean age of 49±11 years. The frequencies of prediabetes and diabetes among study subjects were 48.2% (n=216) and 20.5% (n=92), respectively. There were no significant differences between non-diabetic, prediabetic and diabetic individuals with respect to the following variables; age, gender, BMI, serum levels of HDL-C and thyroid stimulating hormone (TSH). There were statistically significant differences in the SBP, DBP, HbA1c, FPG, 2-h plasma glucose, TC, TG, LDL-C levels and AIP between three groups. Overall, 26.1% (n=112) were found to have elevated blood pressure levels (SBP ≥140 mmHg, DBP ≥90 mmHg).

AIP was calculated for all study subjects (n=448), they were then categorized into three groups based on AIP. Overall, 52.7% of the subjects were in low-risk group (AIP <0.11), 12.5% were in intermediate-risk group (AIP 0.11 to 0.21) and 34.8% were in high-risk group (AIP>0.21). As shown in Table 2, a significant increase was observed in SBP, DBP, HbA1c, FPG and 2-h plasma glucose levels in parallel to increase in AIP risk groups.

Table 3 shows the distribution of subjects based on AIP risk groups and diabetes status. AIP risk group status was significantly associated with diabetes status (p<0.001). For instance, prediabetic individuals were more likely to be in AIP high-risk group compared to non-diabetic individuals (34.3% vs. 22.9%, p<*0.04*). Similarly, individuals with diabetes were more likely to be in AIP high-risk group compared to those with prediabetes (54.3% vs. 34.3%, p=*0.002*).

Table 1. Clinical characteristics of study sample categorized according to diabetes status.

Parameters	Non-diabetic Group (n=140)	Prediabetic Group (n=216)	Diabetic Group (n=92)	p
Age (years)	46.84±9.67	49.06±11.75	50.10±10.46	0.056
Female/Male	119/21	161/55	71/21	0.062
BMI (kg/m^2)	32.47±6.26	32.97±7.06	32.62±6.04	0.783
SBP (mmHg)	118.86±15.52	124.38±19.49	128.48±22.74	0.003*
DBP (mmHg)	73.14±10.33	75.67±10.86	78.32±13.45	0.013*
HbA1c (%)	5.26±0.28	5.71±0.34	6.97±1.29	<0.001*
Fasting Plasma Glucose (mg/dL)	87.91±6.88	102.68±12.32	124.71±33.92	<0.001*
2nd hour Plasma Glucose (mg/dL)	99.28±24.26	135.63±36.21	227.00±66.54	<0.001*
TSH (mIU/L)	2.04±1.45	2.17±2.78	1.78±1.51	0.122*
Total cholesterol (mmol/L)	5.11±1.02	5.55±1.07	5.93±1.10	<0.001
Triglyceride (mmol/L)	1.41±0.68	1.79±0.99	2.51±2.19	<0.001*
LDL- cholesterol (mmol/L)	3.24±0.85	3.49±1.01	3.62±0.80	0.005
HDL- cholesterol (mmol/L)	1.28±0.50	1.26±0.28	1.19±0.31	0.158
AIP (log[TG/HDL-C])	0.02±0.26	0.11±0.26	0.26±0.27	<0.001

SBP; Systolic blood pressure, DBP; Diastolic blood pressure, AIP; Atherogenic index of plasma, TSH; Throid Stimulating Hormone.
* Kruskal-Wallis Test

Table 2. Clinical characteristics of study sample categorized according to AIP.

Parameters	Low Risk (AIP<0.11) (n=236)	Intermediate Risk (AIP=0.11-0.21) (n=56)	High Risk (AIP >0.21) (n=156)	p
Age (years)	48.44±11.39	48.52±9.41	48.79±10.77	0.952
BMI (kg/m^2)	32.73±6.96	33.24±6.06	32.58±6.30	0.822
SBP (mmHg)	120.13±17.76	127.05±19.70	127.31±20.73	<0.001*
DBP (mmHg)	73.79±10.97	76.52±10.87	77.50±11.92	0.006*
HbA1c (%)	5.67±0.71	5.94±1.16	6.04±0.98	<0.001*
Fasting Plasma Glucose (mg/dL)	98.64±16.64	105.79±27.95	107.41±25.80	<0.001*
2nd hour Plasma Glucose (mg/dL)	130.91±53.44	149.41±66.24	159.10±67.46	<0.001*
Total cholesterol (mmol/L)	5.13±0.97	5.70±0.96	5.98±1.14	<0.001
LDL cholesterol (mmol/L)	3.21±0.81	3.74±0.81	3.68±1.05	<0.001

* Kruskal-Wallis Test

As shown in Table 4, AIP was significantly correlated with SBP, DBP, HbA1c, FPG and 2-h plasma glucose levels. Linear regression analysis was also performed to define the variables of AIP (Table 5). Age, BMI, sex, SBP, DBP, HbA1C, FPG, 2-h plasma glucose levels were included in this model. Male sex, BMI, DBP, HbA1c and 2-h plasma glucose levels were determined to be independently associated with AIP.

DISCUSSION

Diabetes mellitus is an independent risk factor for CAD and has a strong relationship with atherogenic dyslipidemia. Atherogenic dyslipidemia was characterized by low levels of HDL-C (less than 40 mg/dL in men and less than 50 mg/dL in women), high levels of TG (>150 mg/dL), and elevated low-density lipoprotein particle number (11). Increased number of smaller LDL and HDL particles has been associated with increased cardiovascular risk, whereas increased number of larger HDL particles has been associated with lower cardiovascular risk (3, 11-16). Therefore, measurement of lipoprotein particle sizes has been recommended for more accurate estimation of car-

Table 3. Distribution of study sample according to diabetes status and AIP risk groups.

Parameters	Low Risk (AIP<0.11) (n=236)	Intermediate Risk (AIP=0.11-0.21) (n=56)	High Risk (AIP >0.21) (n=156)
Non-diabetic Group (n=140) n(%)	92 (65.7%)	16 (11.4%)	32 (22.9%)
Prediabetic Group (n=216) n(%)	114 (52.8%)	28 (13.0%)	74 (34.3%)
Diabetic Group (n=92) n(%)	30 (32.6%)	12 (13.0%)	50 (54.3%)

Chi-Square test (p<0.001).

Table 4. Bivariate correlation results between AIP and other significant parameters in all participants.

Parameters	Correlation Coefficient	p
SBP (mmHg)	0.143	0.002
DBP (mmHg)	0.125	0.008
HbA1c (%)	0.330	<0.001
Fasting Plasma Glucose (mg/dL)	0.269	<0.001
2nd hour Plasma Glucose (mg/dL)	0.246	<0.001

Table 5. Linear regression analysis for covariates of AIP.

Parameters	Standardized Beta‡	t	95% CI
Step 1			
BMI (kg/m^2)	0.088	1.846	0.000/0.007
Age (years)	-0.046	-0.968	-0.003/0.001
Sex	0.224	4.673	0.087/0.212
SBP (mmHg)	0.061	0.765	-0.001/0.003
DBP (mmHg)	0.072	0.909	-0.002/0.005
HbA1c(%)	0.141	1.796	-0.004/0.089
Fasting Plasma Glucose (mg/dL)	0.026	0.340	-0.001/0.002
2nd hour Plasma Glucose (mg/dL)	0.157	2.325	0.000/0.001
r^2=0.150, Adjusted r^2=0.134, p<0.001			
Parameters	**Standardized Beta‡**	**t**	**95% CI**
Step 4			
BMI (kg/m^2)	0.087	1.848	0.000/0.007
Sex	0.220	4.642	0.085/0.210
DBP (mmHg)	0.115	2.489	0.001/0.005
HbA1c(%)	0.152	2.356	0.008/0.084
2nd hour Plasma Glucose (mg/dL)	0.165	2.555	0.000/0.001
r^2=0.147, Adjusted r^2=0.137, p<0.001			

diovascular disease risk (3, 17). It is well known that higher AIP can be used as a surrogate for smaller size of both HDL and LDL particles (3, 5, 6, 18). Additionally, the significant association between TG/HDL-C ratio and CAD has been confirmed by several studies (19-24).

Previous studies showed that TG/HDL-C ratio predicts glucose disposal rate and Homeostasis Assessment Model values in non-diabetic overweight and obese postmenopausal women (25). Furthermore, AIP has been associated with impaired FPG (7), gestational diabetes mellitus (26, 27), insulin resistance (8, 28, 29) and epicardial adipose tissue (30). Li et al. (31) showed that AIP was a useful indicator for insulin resistance across different ethnicities.

The major findings of this study were as follows: first, higher AIP values were significantly associated with abnormal glucose metabolism parameters such as elevated HbA1c, FPG, and 2-h plasma glucose levels. Among all parameters, HbA1c had the strongest correlation with AIP. Consistently, AIP was significantly associated with diabetes status among the study subjects. For instance, average AIP showed an increasing trend from non-diabetics to diabetics (0.02 vs. 0.11 vs. 0.26 in non-diabetics vs. prediabetics vs. diabetics). Similarly, compared to those with prediabetes, diabetics were more likely to be in AIP high-risk group. Also subjects with prediabetes were more likely to be in AIP high-risk group compared to non-diabetics. Consistent with previous studies, AIP risk group status was also significantly associated with other cardiovascular risk factors among the subjects. For instance, linear regression analysis revealed that higher AIP was independently associated with male sex, BMI, DBP, HbA1c and second hour plasma glucose levels. To our knowledge, this was the first study evaluating the relationship between AIP and diabetes status determined by a comprehensive evaluation (FPG, OGTT, and HbA1c).

Although this data was collected prospectively, because of the cross-sectional study design, it cannot be determined whether high AIP contributed to or was a consequence of impaired glucose metabolism. However, the association between high AIP and diabetes can be attributed to several pathways involved both in glucose and lipid metabolism. Several previous studies suggested that insulin resistance and chronic inflammation were the most likely mechanisms underlying the association between high AIP and abnormal glucose metabolism (8, 25, 28, 29, 31).

The results of this study should be interpreted in the context of several limitations. First, these findings were limited to a single center in Turkey, and should be confirmed with a larger, multicenter study. Second, this sample size was modest and male subjects were underrepresented in this study. Further studies with larger sample sizes will be helpful to examine sex-specific relationship between AIP and glucose metabolism. Finally, a case-and-effect relationship cannot be determined given the cross-sectional nature of this study.

In conclusion, AIP was significantly association with parameters of diabetes and metabolic syndrome. In this perspective, higher AIP might be a sign of prediabetes, diabetes, metabolic syndrome, more atherogenic lipid profile and probable existing CAD. This index might be helpful to more accurately evaluate cardiovascular risk in diabetic patients. In addition, diabetes screening should be considered in individuals with elevated AIP and no known history of diabetes. Further prospective and multicentric studies will be needed to shed more light on the relationship between AIP and diabetes.

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Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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