ORIGINAL ARTICLE

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Role of Insulin Resistance in the Development of Atrial Fibrillation

Atriyal Fibrilasyon Gelişiminde İnsülin Direncinin Rolü

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ABSTRACT

Aim: To investigate the relationship between insulin resistance (IR) and atrial fibrillation (AF) in patients without overt diabetes.

Materials and Methods: Patients aged ≥18 years without chronic disease other than hypertension were included in the study. Medical histories were obtained, and detailed physical examination, blood tests and electrocardiography were performed. Patients with overt diabetes were excluded from the study. The patients were evaluated in two groups [normal sinus rhythm (NSR) and AF groups]. The presence of IR was analyzed.

Results: Two hundred patients (the mean age, 67.33±8.37 years; 108 females), of whom 132 (66%) had NSR and 68 (34%) had AF, were included in the study. There was no difference between the groups regarding fasting plasma glucose levels (102.65±7.49 mg/dL and 99.68±9.46 mg/dL, respectively; p=0.09). A significant difference was found regarding fasting insulin levels (11.06±2.71 mg/dL and 8.48±2.64 mg/dL, respectively; p<0.0001). The mean IR [homeostatic model assessment (HOMA-IR)] was significantly higher in the AF group than in the NSR group (2.90±0.79 and 2.10±0.46, respectively; p<0.0001). The proportion of patients with IR (HOMA-IR >2.4) was significantly higher in the AF group than in the NSR group (76.47% and 28.78%, respectively; p<0.0001). Regression analyses were performed. Multivariate regression analysis showed that each unit increase in HOMA-IR increased the risk of AF for 2.56-fold.

Conclusion: The main factor for the frequent coexistence of diabetes mellitus and AF was considered to be IR rather than hyperglycemia. Early detection and treatment of IR can reduce AF development and associated morbidity and mortality.

Keywords: Diabetes mellitus, insulin resistance, arrhythmia, atrial fibrillation

ÖZ

Amaç: Çalışmamızın amacı aşikar diyabeti olmayan hastalarda insülin direncinin (IR) atriyal fibrilasyon (AF) ile ilişkisini araştırmaktır.

Gereç ve Yöntem: Çalışmamıza 18 yaş ve üzeri hipertansiyon dışında kronik hastalığı olmayan hastalar dahil edildi. Hastaların tıbbi öyküleri alındı, fizik muayeneleri ve kan tahlilleri yapıldı ve elektrokardiyografileri çekildi. Tetkiklerinde aşikar diyabet saptanan hastalar çalışma dışı bırakıldı. Hastalar normal sinüs ritminde (NSR) olan grup ve AF'si olan grup olmak üzere ikiye ayrıldı ve IR analiz edildi.

Bulgular: Çalışmaya 132'si (%66) NSR'de ve 68'i (%34) AF ritminde olan toplam 200 hasta (108 kadın, yaş ortalaması 67,33±8,37 yıl) dahil edildi. NSR'de ve AF ritminde olan hastalar arasında açlık plazma glikoz seviyeleri açısından fark bulunmazken (sırası ile 102,65±7,49 mg/dL ve 99,68±9,46 mg/dL; p=0,09), açlık insülin düzeyi açısından anlamlı bir fark tespit edildi (sırasıyla 11,06±2,71 mg/dL ve 8,48±2,64 mg/dL; p<0,0001). İnsülin direnci [homeostatik model değerlendirmesi (homeostatic model assessment HOMA-IR)] ortalaması AF grubunda NSR grubuna göre anlamlı düzeyde yüksek tespit edildi (sırası ile 2,90±0,79 ve 2,10±0,46; p<0,0001). İnsülin direnci olan (HOMA-IR >2,4) hastaların oranı AF grubunda NSR grubuna göre anlamlı olarak daha yüksek bulundu (sırasıyla %76,47 ve %28,78; p<0,0001). Regresyon analizleri yapıldı. Çok değişkenli regresyon analizi HOMA-IR'deki her bir birimlik artışın AF riskini 2,56 kat artırdığını gösterdi.

Sonuç: Diyabet ve AF birlikteliğinin sık görülmesinde ana faktörün hiperglisemiden çok, öncesinde gelişen IR olduğu düşünülmüştür. IR'nin erken tespiti ve tedavisi, AF gelişimini ve ilişkili morbidite ve mortaliteyi azaltabilir.

Anahtar Kelimeler: Diyabet, insülin direnci, aritmi, atriyal fibrilasyon

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INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a worldwide prevalence of 2%[1]. AF is associated with increases in the rates of ischemic stroke, cardiac failure, and mortality. Diabetes mellitus (DM) is one of the most important risk factors for AF. A meta-analysis of cohort and case-control studies has demonstrated that patients with DM have a 40% higher risk of AF, compared to patients without DM[2]. Before overt DM occurs, insulin resistance (IR) and prediabetes stages are passed, but these stages may not be noticed because they are silent. Recent studies have suggested IR as a risk factor responsible for the development of AF[3]. The relationship between DM and AF has been demonstrated, but it is controversial whether the cause is hyperglycemia after overt diabetes develops or IR that develops much earlier. The aim of our study is to reveal the relationship between IR, which is a modifiable risk factor, and AF.

MATERIALS AND METHODS

Our study was approved by İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (decision number: 77, approval date: 21.01.2021) and conducted in accordance with 1975 Helsinki Declaration and its amendment in 2013. The study was conducted in the Internal Medicine Clinic of İstanbul Medipol University Medical Faculty Hospital between the dates of January 2020-June 2021. The patients were informed about the study and a consent form was signed. Patients aged 18 years and older, who had systolic blood pressure above 140 mmHg, diastolic blood pressure above 90 mmHg after two measurements during our examination, or who were using antihypertensive medication, were included in the study. For the power analysis, the study of Lee et al.[4] was taken as reference. Considering the prediction between the new-onset AF and high homeostatic model assessment for insulin resistance (HOMA-IR) with hazard ratio=1.61, 95%, confidence interval=1.14-2.29 and p=0.007, the sample size per group was calculated as minimum 60, with a type 1 error of 0.05 and the strength of the study being 80%. With a 20% loss, a total of 200 patients were incorporated in the study. Medical histories of the patients were taken, and detailed physical examination including weight, height and body mass index (BMI, kg/m^2) was performed. Blood tests including fasting plasma glucose, fasting insulin, HOMA-IR, hemoglobin A1c, lipid profile, kidney and liver functions, thyroid functions, serum electrolytes and electrocardiograms were taken. Patients with secondary hypertension, known diabetes, and fasting blood sugar of ≥126 mg/dL, those using antidiabetic drugs, uncontrolled thyroid patients, those with known cardiovascular disease or heart failure, those receiving oncological treatment, those with neurological disease and those who did not want to participate in the study were excluded from the study. The patients were divided into two groups as the normal sinus rhythm (NSR) group and AF group and analyzed for the presence of IR. Patients with a HOMA-IR value >2.4 were considered IR.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 15.0 (SPSS, Inc., Chicago, IL, USA). Continuous and quantitative variables were expressed as mean and standard deviation. The chi-square analysis was performed for discrete qualitative variables. Unpaired Student's t-test was used to analyze continuous variables. The correlation between the presence of AF and the presence of IR was evaluated and the Pearson's number (r value) was recorded. A correlation above 30% was considered a significant relationship. A p value of <0.05 was considered statistically significant. Univariate and multivariate logistic regression analyses including HOMA-IR, BMI, age, and gender were performed.

RESULTS

The present study included 200 patients (108 females, 92 males) with a mean age of 67.33±8.37 years. The proportion of patients with NSR was 66% (n=132; 72 females, 60 males) and the proportion of patients with AF was 34% (n=68; 36 females, 32 males). The mean age was 66.41±8.58 years for the patients with AF and 67.80±8.29 years for those with NSR. The demographic characteristics and findings of study parameters

Table 1. Demographic characteristics and findings of study parameters in the study groups

	AF n=68	Patients with NSR n=132	p
Female/male, n/n	36/32	72/60	0.23
Mean age, years, mean±SD	66.41±8.58	67.80±8.29	0.44
Fasting blood glucose level, mg/dL, mean±SD	102.65±7.49	99.68±9.46	0.09
Fasting insulin level, mg/dL, mean±SD	11.06±2.71	8.48±2.64	<0.0001
Patients with IR (a HOMA-IR of >2.4), n (%)	52 (76.5)	38 (28.8)	<0.0001
Mean HOMA-IR, mean±SD	2.90±0.79	2.10±0.46	<0.0001
Body mass index	30.43±3.89	26.18±5.32	<0.0001

AF: Atrial fibrillation, NSR: Normal sinus rhythm, n/n: Number/number, SD: Standard deviation, IR: Insulin resistance, HOMA-IR: Homeostatic model assessment for insulin resistance

(age, gender, fasting plasma glucose level, fasting insulin level, BMI and HOMA-IR value) in the NSR and AF groups are presented in Table 1. No significant difference was found between the patients with NSR and AF in terms of age and sex distribution (p=0.44 for age and p=0.23 for sex). While no significant difference was found between the patients with AF and NSR in terms of fasting plasma glucose level (102.65±7.49 mg/dL and 99.68±9.46 mg/dL, respectively; p=0.09), there was a significant difference between the patients with AF and NSR in terms of fasting insulin level (11.06±2.71 mg/dL and 8.48±2.64 mg/dL, respectively; p<0.0001) and HOMA-IR value (2.90±0.79 and 2.10±0.46, respectively; p<0.0001). IR was found in 38 (28.8%) of 132 patients with NSR and 52 (76.5%) of 68 patients with AF; the proportion of patients with IR was significantly higher in the patients with AF (p<0.0001). A positive significant correlation was found between AF and HOMA-IR (r=0.43, p<0.0001). The mean BMI was 30.43±9.89 kg/m^2 for the patients with AF and 26.18±5.32 kg/m^2 for the patients with sinus rhythm. A significant positive correlation was found between AF and BMI (r=0.33, p<0.05). Moreover, a significant positive correlation was also revealed between fasting blood glucose, fasting insulin, HOMA-IR and BMI (r=0.39, p<0.0001, r=0.62, p<0.0001 and r=0.62, p<0.0001, respectively). The effect of age, fasting blood glucose, fasting insulin level, HOMA-IR and BMI on AF were evaluated by using univariate logistic regression. Fasting blood glucose, fasting insulin level, HOMA-IR and BMI were found to be significant. HOMA-IR was calculated from fasting blood level and fasting insulin level; therefore, only HOMA-IR and BMI parameters were included in the multivariate logistic regression analysis to avoid multicollinearity. According to the multivariate logistic regression model, only HOMA-IR affects AF. Each "1" unit increase in HOMA-IR causes 2.56 times more AF (Table 2).

DISCUSSION

Patients with DM are at high risk for developing AF and AF-related morbidity and mortality[5]. It is controversial whether the reason for the frequent occurrence of AF in diabetic patients is hyperglycemia that occurs after the development of overt diabetes or IR that occurs much earlier. In recent years, studies have been conducted suggesting that the main cause is IR[6,7]. Accordingly, we aimed to investigate whether hyperglycemia or a much earlier IR was the predominant factor in the development of AF and therefore only patients with IR were included in this study and patients with overt DM were excluded. AF is the most common arrhythmia in the world and its incidence increases with age. Hypertension and AF are frequently seen together due to both having common risk factors and common mechanisms involved in the pathogenesis[8]. Left ventricular hypertrophy and left atrial remodeling caused by hypertension are thought to be responsible for the development of AF[9]. All of 200 patients included in our study were hypertensive and their mean age was high (67.33±8.37 years), so we detected a high rate of AF (34%). In this study, when the group with AF and the group with NSR were compared, no significant difference was found between the two groups in terms of age, gender, and mean fasting blood sugar. The mean of BMI, fasting insulin and HOMA-IR were found to be significantly higher in the group with AF. When the multivariate logistic regression analysis was evaluated, it was determined that only HOMA-IR affected AF. According to the result of the analysis, every 1 unit increase in HOMA-IR value causes 2.56 times more AF. Before the appearance of overt DM, the IR phase is passed. Increased free fatty acid levels (lipotoxicity) and hyperglycemia (glucotoxicity) in the circulation due to overnutrition, sedentary life and metabolic disorders are the factors that initiate and maintain IR. A prospective study was conducted to investigate the contribution of IR to the risk of long-term incidence of AF in 8,175 subjects. Subjects without DM and AF were initially included in the study and were followed up for AF development at biennial controls. During a median follow-up of 12.3 years, 136 subjects developed AF (incidence ratio: 1.89/1,000 patient-years) and it was reported that patients with IR had a 60% higher risk of developing AF than those without[4].

The Action to Control Cardiovascular Risk in Diabetes study found that aggressive DM management aimed at maintaining HbA1c <6% and failed to reduce the incidence of AF compared to a standard therapy targeting HbA1c 7.0-7.9%[10]. These studies suggest that the main factor in the development of AF is IR rather than hyperglycemia. Pathophysiologically, changes due to IR including inflammation, endothelial dysfunction, and

Table 2. Evaluation of parameters affecting AF

	Univariate logistic regression			Multivariate logistic regression		
	B	OR	p	B	OR	p
Age	-0.020	0.90 (0.95-1.02)	0.265	-	-	-
Fasting blood glucose	0.089	1.09 (1.05-1.13)	**<0.001**	-	-	-
Fasting insulin level	0.337	1.4 (1.24-1.58)	**<0.001**	-	-	-
HOMA-IR	1.111	3.04 (2.06-4.47)	**<0.001**	0.938	2.56 (1.59-4.12)	**<0.001**
BMI	0.126	1.13 (1.07-1.20)	**<0.001**	0.041	1.04 (0.97-1.12)	0.254

OR: Odds ratio with 95% confidence interval (lower-upper limit), BMI: Body mass index, HOMA-IR: Homeostatic model assessment for insulin resistance

myocardial steatosis lead to atrial dilatation and structural and electrical remodeling and thereby results in AF[11].

In a study conducted on rats to examine the relationship between IR and AF at the cellular level, it was revealed that IR was associated with various aspects of atrial remodeling, including increased oxidative stress, increased intracellular calcium, increased interstitial fibrosis, and increased risk of arrhythmia[12]. After demonstrating the relationship between IR and AF development, studies focused on whether agents that break IR could reduce the incidence of AF development. In a meta-analysis, it was shown that thiazolidinones led to a 30% reduction in the risk of developing AF[13]. In a study conducted in Thailand, newly diagnosed type 2 DM patients who received metformin monotherapy were compared with those who did not receive drug therapy, and it was found that metformin reduced the rate of development of AF in diabetic patients[14]. These studies have shown that oral antidiabetic agents, which break IR, can prevent atrial myocyte structural remodeling by reducing intracellular oxidative stress and improving IR may be effective in preventing AF in patients with prediabetes[15]. In our study, no gender difference was found between patients with NSR and those with AF. A cohort study on more than 15,000 participants, followed for nearly 30 years, showed that the lifetime risk of developing AF was 30% in women and 36% in men[16]. The incidence of AF is lower in women, but the prevalence of AF is higher in women when men and women over 75 years of age are compared. AF rates are similar in men and women due to increased life expectancy[17,18]. In our study, it was thought that the reason why there was no significant difference between the two groups in terms of gender was the high mean age of the participating patients. IR almost always accompanies obesity, and many studies have shown a relationship between obesity and AF[19-21]. In a meta-analysis including 16 studies, it was found that the risk of AF increased by 49% in individuals with a BMI above 30 kg/m^2 [22]. Another study reported that weight management provided beneficial cardiac remodeling and a reduction in AF burden and severity[23]. In our study, the mean BMI value was calculated as 30.4 kg/m^2 in patients with IR and as 26.2 kg/m^2 in patients without IR. Consistent with these studies, AF was detected more frequently in patients with high BMI and IR in our study.

Study Limitations

Our study has some limitations. Firstly, it is a single-center study conducted on 200 patients. There is a need for multicenter studies with more patients on the subject. The second limitation of the study is that instant electrocardiography was taken from the patients. This may have caused us to miss patients with paroxysmal AF. Finally, the third limitation of the study is that it is a cross-sectional study. The presence of AF and IR were examined simultaneously. Therefore, although we found a significant positive correlation between these two conditions, it is difficult to clearly reveal the causal relationship. It would be beneficial to conduct large-scale cohort studies that clearly reveal the cause and effect relationship on the subject.

CONCLUSION

Our study has shown that each unit increase in IR increases the risk of AF 2.56 times. The relationship between DM and AF is clear; however, the results of our study suggest that hyperglycemia has a minor role in this relationship contrary to what was previously suggested, and the main reason was thought to be IR developed much earlier. Early detection and treatment of modifiable risk factors such as IR responsible for the development of AF can reduce the risk of developing AF, which causes serious morbidity and mortality.

Ethics

Ethics Committee Approval: This study was approved by İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (decision number: 77, approval date: 21.01.2021).

Informed Consent: The patients were informed about the study and a consent form was signed.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.E., Concept: E.Y., Design: E.Y., Data Collection or Processing: D.E., Analysis or Interpretation: E.Y., Literature Search: E.Y., Writing: E.Y., D.E.

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