ORIGINAL ARTICLE

GMJ.2021;10:e2106
www.gmj.ir

Received 2020-12-22
Revised 2021-01-26
Accepted 2021-02-25

Association Between Permanent Non-Valvular Atrial Fibrillation with Microalbuminuria and C-Reactive Protein

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Abstract

Background: An understanding of atrial fibrillation (AF) mechanisms, as the most common cardiac arrhythmia, is essential for primary and secondary prevention. Some studies indicated an association between microalbuminuria and C-reactive protein (CRP) protein, with the incidence and prevalence of AF. This study aimed to investigate the relationship between permanent non-valvular AF with microalbuminuria and reactive protein C. **Materials and Methods**: In this case-control study, 40 permanent non-valvular AF patients and 40 non-AF patients (control group) were studied. Demographic data and measurements of albumin, urine creatinine, CRP, and microalbuminuria were recorded and compared between the two groups. **Results**: In patients with permanent non-valvular atrial fibrillation, CRP level (P<0.001) and microalbuminuria (P=0.012) were significantly higher than the control group. Also, in patients with permanent non-valvular AF, the CRP positive (P = 0.014) and microalbuminuria (P = 0.003) were significantly higher than controls. The results showed that elevated chance of permanent non-valvular AF with abnormal CRP was 4.25 (odds ratio [OR]= 4.25, 95% confidence interval [CI]: 1.18-1.28; P= 0.026), and with microalbuminuria was 6.54 (OR= 6.54, 95% CI: 1.65-25.89; P=0.007). **Conclusion**: An elevated CRP level and microalbuminuria were significantly associated with permanent non-valvular atrial fibrillation. A longitudinal study is necessary.

[GMJ.2021;10:e2106] DOI:10.31661/gmj.v10i0.2106

Keywords: Non-Valvular Atrial Fibrillation; Microalbuminuria; C-Reactive Protein

Introduction

Atrial fibrillation (AF) is one of the permanent disorders of heart rhythm that is associated with several problems in the individual [1].

AF is the most common cardiac arrhythmia and is associated with an increased risk of stroke and could even cause death [2].

Despite the significant advances in prevention, AF is still associated with a relatively high risk, which leads to multiple complications, recurrent hospitalizations, reduced quality of life, and even death [1]. This disorder has become one of the most important causes of hospitalization and severe health

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risks, and the resulting costs could cause irreparable damage to the health system of any society [3, 4]. Some studies have been mentioned as one of the most important causes of mortality and morbidity in patients [5]. Therefore, the need for planning to perform primary and secondary preventions is essential. It requires a better understanding of the potential underlying mechanisms that cause AF [6-7]. Microalbuminuria is defined as the excretion of albumin at a rate of 30 to 300 mg/dL in 24-hour urine, which could be used as an indicator of damage or endothelial dysfunction of all arteries in the body, including ischemic heart disease, diastolic heart failure, and congestive heart failure [8]. This criterion could be an independent risk factor for inducing heart diseases, such as atherosclerosis [9-10]. The relationship between microalbuminuria and AF has been studied in some research, and the results show that microalbuminuria, as an independent factor, could predict the prevalence of AF [11]. In one study, the prevalence of microalbuminuria was about 10 percent higher in people with a history of AF than in those without AF [8]. In this regard, the results of various studies have shown the association of various inflammatory factors, such as C-reactive protein (CRP), with the occurrence and enhancement of AF [12-14]. Inflammation could be considered as a predictor of subclinical heart diseases by inducing structural and electrical regeneration of the atrium and vascular dysfunction [15]. A study by Asselbergs *et al*. [15] in the Netherlands indicates a strong association between increased CRP levels and microalbuminuria with AF.

After combining the CRP results with microalbuminuria, the highest association with AF was observed [15].

Studies on the association between atrial fibrillation and microalbuminuria and CRP levels and the simultaneous effect of microalbuminuria and CRP on AF are limited, not only in Iran but in the world, and further studies are necessary in this regard.

Therefore, this study aimed to determine the association between permanent non-valvular AF with microalbuminuria and CRP level and investigate the prevalence of microalbuminuria among patients with permanent non-valvular AF.

Materials and Methods

Patients

This case-control study was performed on the 80 patients who were referred to the cardiology ward of Kowsar Hospital, Semnan, Iran and a private heart clinic (Semnan, Iran) from 2019 to 2020.

Sample Size Calculation

Given the fact that there are a small number of studies with a similar topic to our study and the sample size of each group was 30 people; in the form of a pilot study with a 25% probability of sample drop, samples were finally determined to be 40 patients with permanent non-valvular AF and 40 non-AF patients (control group).

Inclusion and Exclusion Criteria

Patients with permanent non-valvular AF were selected using the simple sampling method.

The control group (without AF) was also selected from all outpatients without permanent non-valvular AF referred to a private heart clinic.

Matching was done between the case and control groups in terms of age (± five years). Patients with microalbuminuria distorters (e.g., uncontrolled hypertension), macroalbuminuria, intake medication during the last six months (including insulin, cimetidine, non-dihydropyridine calcium channel blockers, angiotensin-converting enzyme inhibitors, penicillin, sulfonamides, and losartan), systemic diseases (especially chronic heart failure), serum creatinine higher than 20 mg/L, hematuria, pregnancy, acute urinary tract infection, acute fever greater than 38 °C, diabetes, intense exercise in the last 24 hours, receiving radiocontrast, CRP level disrupting conditions (including acute or chronic inflammatory conditions, tissue injury or necrosis, ischemia or tissue infarction, infection, metabolic syndrome, acute pancreatitis, burns), leukemia, hormone therapy, recent surgery, malignant tumors (especially breast, lung and gastrointestinal tract), weight loss, and moderate alcohol consumption [8, 15] were excluded from the study.

Data Collection

Baseline information of patients included age, gender, body mass index (BMI), smoking history, and laboratory data (including urinary albumin levels, urinary creatinine measurement, and CRP level) were recorded.

Measurement of the patient's blood pressure was performed after 5 minutes of rest, from the brachial artery, with the help of a mercury barometer to millimeters of mercury, and in a sitting position using a single barometer. At the next visit, a sample of fasting blood and a sample of morning urine were taken from all participants. Also, patients were advised not to eat a high-protein diet the day before the test and follow a light diet. Urine albumin and creatinine were measured using quantitative albumin and creatinine detection kits (Bionic Company), respectively. Microalbuminuria was calculated using the urinary albumin-to-creatine ratio (UACR) index based on the division of random urinary albumin in milligrams by the amount of random urinary creatinine in grams. Accordingly, values between 30 and 300 mg/g were considered as microalbuminuria. CRP measurement was performed by serum or plasma CRP quantitative detection kit (Pars Azmoun Co., Iran) with the enhanced immunoturbidimetry method for a one-point measurement with a photometer. TruCal CRP calibrator was used for calibration, and Trulab Protein (Pars Azmoun Co., Iran) was used separately for control. Finally, the indicators and laboratory information were evaluated and compared between the two groups of case and control.

Ethical Consideration

This study was approved by the Ethical Committee of Semnan University of Medical Sciences (ethics code: IR.SEMUMS.REC.1397.99). Also, written informed consent was taken from the patients prior to the study. No negative interventions or inappropriate changes were imposed on individuals in the study process, and patients were not deprived of their standard treatment.

Statistical Analysis

Data were recorded in a pre-compiled collection checklist by research colleagues and entered into SPSS statistical analysis software version 23 (). Data analysis was performed using Shapiro-Wilk, t-test (or Mann-Whitney U), chi-square, and logistic regression tests. The significance level was considered at P=0.05.

Results

The mean age of patients with permanent non-valvular AF was 66.7±10.8 years (ranged 46-87), and in the control group was 63.2±8.9 years (ranged 49-81), but the difference was not significant (P=0.118). Also, 57.5% (23) of patients with permanent non-valvular AF and 52.5% (21) of the control group were male, which indicated no significant difference (P = 0.563). The mean BMI in case and control groups was 27.5±2.6 kg/m2 and 26.5±2.5 kg/m2, respectively (P = 0.087). In addition, 82.5% of patients with permanent non-valvular AF and 80.0% of controls were overweight or obese.

Five patients (12.5%) with permanent non-valvular AF and eight patients (20%) of the control group were smokers (P =0.363). The mean number of cigarettes consumed among patients with permanent non-valvular AF was 4.5±1.6 pack/years, and in the control group was 4.6±2 pack/years.

The mean CRP level of patients with permanent non-valvular AF was 7.7±2.9 mg /l and in the control group was 4.4±3.4 mg /l that showed a significant difference between the two groups (P<0.001).

Also, 32.5% (13) of the patients with permanent non-valvular AF and 10% (4) of the control group were CRP + (≥8 mg/l), which indicated a significant difference between the two groups (P=0.014, Table-1).

The mean microalbuminuria in patients with permanent non-valvular AF was 36.7±8.3 mg/g, while in the control group was 26.8±7.5 mg/g. There was a significant difference in the term of microalbuminuria levels between the two groups (P=0.012).

Fourteen (35%) patients with permanent non-valvular AF and three (7.5%) patients of the control group had microalbuminuria (30-300 mg/g), which indicated a significant dif-

ference between the two groups. (P = 0.003, Table 2). The results of logistic regression showed that abnormal CRP level (odds ratio [OR]= 4.25, 95% confidence interval [CI]: 1.18-1.28; P= 0.026) increased the chances of permanent non-valvular AF by 4.25 times. Also, microalbuminuria (OR= 6.54, 95% CI: 1.65-25.89; P= 0.007) increased the chance of permanent non-valvular AF by 6.54 times.

Discussion

The present study is one of the few studies investigating the association between permanent non-valvular AF with microalbuminuria and CRP. In other words, most studies have examined the association between AF and renal failures in general. The most important strength of this study compared to other studies was its novelty.

The results of the current study showed that the two groups were not significantly different in terms of underlying or confounding variables such as age, gender, BMI, and smoking; therefore, it was possible to more accurately investigate the results related to the study of the association between permanent non-valvular AF with microalbuminuria and CRP.

The mean microalbuminuria in patients with permanent non-valvular AF was significantly higher than the control group that did not have this disorder. The prevalence of microalbuminuria among patients with permanent non-valvular AF was significantly higher than in the control group. Also, the results showed that microalbuminuria increases the chance of permanent non-valvular AF by 6.54 times. In a study by McManus *et al*. [11], the ratio of albumin to urinary creatinine was 10 mg/g (between 6 and 19 mg/g). The results of logistic regression analysis showed that patients with higher urinary albumin to creatinine ratio (greater than 15 mg/g) were four times more likely to develop AF, in comparison with the

Table 1. Distribution of CRP Level and Microalbuminuria in Patients with Permanent Non-Valvular AF and Control Group

Parameters	Groups				P-value
	Case		Control		
	Quantity	Frequency percentage	Quantity	Frequency percentage	
CRP (mg/L)					
Positive (≥ 8)	13	32.5	4	10	0.014
Negative (<8)	17	67.5	36	90	
Albuminuria level (mg/g)					
Normal (<30)	26	65	37	92.5	
Microalbuminuria (30-300)	14	35	3	7.5	0.003

Table 2. Distribution of microalbuminuria in patients with permanent non-valvular atrial fibrillation and control group

Microalbuminuria level (mg/g)	Groups			
	Case		Control	
	Quantity	Frequency percentage	Quantity	Frequency percentage
Normal (<30)	26	65.0	37	92.5
Microalbuminuria (30-300)	14	35.0	3	7.5
Total	40	100	40	100

patients with lower urinary albumin to creatinine ratio (less than 7 mg/g) [11]. The authors indicated that the level of albuminuria in individuals, as an independent factor, could predict the prevalence of AF [11]. These results are consistent with the findings of the present study.

In another study, Böhm *et al*. [8] examined the association between microalbuminuria and AF. The results showed that the prevalence of microalbuminuria, with a significant relation, was about 10% higher in people with a history of AF than people without AF [8]. These results are in line with the present study's findings, with the difference that in our study, the prevalence of microalbuminuria in patients with AF was more than five times higher than in healthy individuals without AF. Asselbergs *et al*. [15] investigated the association of microalbuminuria with AF.

They showed that microalbuminuria was significantly associated with the incidence of AF [15]. These findings were also similar to the results of the present study. However, contrary to the method of the present study, others studies followed patients with albuminuria and non-AF patients. However, similar to the findings of our study, they found that albuminuria was associated with AF. For instance, in a study by Molnar *et al*. (2017) in Canada, albuminuria was assessed as the ratio of urinary albumin to urinary creatinine [16]. This study showed that the mean follow-up period of patients was six years and 44809 patients had AF. In these patients, the severity of albuminuria was associated with an increased risk of AF [16].

Numerous theories have been proposed in various studies on the relationship between microalbuminuria and AF. Several studies have suggested that this criterion could be an independent risk indicator for developing heart diseases, such as atherosclerosis [9, 10]. Another study also states that renal dysfunction leading to albuminuria could develop AF by activating the renin-angiotensin-aldosterone system (RAAS), retaining water and salt, and increasing blood pressure [17]. In addition, the RAAS system, by inducing atrioventricular valve disorders and changes in its electrophysiological role, would be a factor in developing atrial fibrillation [17]. However, in the present study, by selecting patients with non-valvular AF and excluding patients with hypertension, the distorting effects of hypertension and valvular disorders on the incidence of albuminuria were eliminated; thus, the above theories were rejected. Other studies have suggested that people with microalbuminuria may have a history of heart disease as well as related medications, which leads to kidney disorders, consequently, microalbuminuria in the long term [17,18].

Therefore, the incidence of microalbuminuria in patients with AF is not unexpected [17, 18]. This hypothesis in our study, considering the exclusion of patients with other heart disorders as well as users of related drugs, was unable to explain the leading cause of the association between the prevalence of microalbuminuria in patients and AF. Other authors have suggested other theories that AF may have caused albuminuria, not the other way around.

In other words, researchers have shown that AF by reducing cardiac output and the development of prerenal azotemia, causes damage to the glomeruli, consequently, to microalbuminuria over time [18]. However, the exact cause-and-effect relationship between the two has not yet been elucidated, and more studies are needed to evaluate this relationship more accurately.

The present study results showed that the mean CRP level among patients with permanent non-valvular AF was significantly higher than the control group. Also, the prevalence of CRP + cases in patients with permanent non-valvular AF was significantly higher than in the control group. The logistic regression analysis results showed that abnormal CRP increased the chance of developing non-permanent AF by 4.25 times. A study in the Netherlands examined the association between CRP and AF that showed the increase of CRP levels was significantly associated with AF incidence [15].

In addition, the results after controlling for other confounding factors showed that the increase of CRP levels was highly sensitive in the prognosis of AF [15], which is in line with the findings of the present study. In a study by Chung *et al*. [14] in the United States, CRP

levels in 131 patients with atrial arrhythmia were compared with the CRP levels in 71 people without arrhythmia.

Their results showed that CRP levels in patients with atrial arrhythmia were higher than the control group [14]. Patients with permanent AF had higher CRP than patients with paroxysmal AF, and both permanent and paroxysmal AF groups had higher CRP than controls [14], which was consistent with the findings of our study. However, in the current study, only patients with permanent non-valvular AF were included. In a study by Marott *et al*. [19] in Denmark on 47,000 people, the relationship between CRP and AF was examined. They indicated that high levels of serum CRP are strongly associated with an increased risk of AF [19], which was similar to the results of the current study. There are various theories about the association between high serum CRP levels and an increased risk of AF. Some researchers have found the cause of this relationship unknown. For instance, Chung *et al*. [14] reported that although the cause of increased CRP levels in AF patients was unknown, an increase in CRP indicates an inflammatory condition that may enhance AF persistence [14].

Another study found that many patients with AF gradually developed some degree of fibrosis with degeneration of the atrial muscles, sinus nodes, and/or interstitial communication pathways; therefore, inflammatory factors (e.g., CRP levels) increase in them [20]. Many other studies have suggested other theories that inflammation has been implicated in the pathogenesis of AF, which means that inflammation has caused AF and not the other way around [21]. In another study, Gur *et al*. (2018) in Turkey concluded that inflammatory factors, especially increased CRP levels, were strongly associated with AF in cardiac patients [22].

Therefore, it appears that by following patients with AF and performing serial tests related to inflammatory factors, especially repeated evaluation of CRP levels in these patients, the cause and effect role between inflammatory factors and AF could be reported more accurately. Because studies with this method have found that the increased CRP levels in patients with AF, at least after two weeks of normalization of the rhythm, have returned to normal and initial levels [23]. An important point and strength that was addressed in our study were patients with non-valvular AF were examined.

In contrast, several authors attributed the increase of CRP levels in patients with AF to only valvular changes and heart valve dysfunctions in AF patients. Even by eliminating the distorting risk factors, a statistically significant relationship was noted between the valvular dysfunctions and increased levels of CRP [24]. Therefore, our study rejects the hypothesis that valvular disorders in patients with AF may have increased the CRP levels and recommends that other researchers conduct further studies to collect more precise and better findings.

In addition to the strengths of this study, we had some limitations. There are certainly many known and unknown factors that may influence the association between permanent non-valvular AF with microalbuminuria and CRP, and indeed, the evaluation of all of these factors, especially nutrition, genetics, and the method of controlling metabolic disorders, are not possible in one study and would require more studies in a wider statistical population.

It is suggested that in future studies, with specific interventions, it would be determined whether the treatment of AF could reduce microalbuminuria and inflammatory factors or vice versa.

Also, it is recommended that cellular and molecular studies be performed to identify the pathogenesis and the causes of association between permanent non-valvular AF with microalbuminuria and CRP.

So that therapists could identify this association and plan their treatment protocols with more attention and accuracy. It is also recommended to study other inflammatory factors, especially in serial studies at more extended periods, to clarify this relationship.

Conclusion

Our study indicated that the rate of microalbuminuria and serum CRP levels in patients with permanent non-valvular AF were higher than

the control group, and possibly, higher microalbuminuria and serum CRP levels would cause more prevalence of permanent non-valvular AF.

Acknowledgments

This study was derived from the thesis of Dr. Maryam Niknahad that supported by the Research Council of Semnan University of Medical Sciences (grant number: 1434).

Conflict of Interest

The authors declare there were no any conflicts of interest.

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